

ISBN: 978-81-954602-4-3

**Endophytes:
Novel Microorganisms for Plant Growth Promotion**

First Edition

Editors

**Ms. Sonali Priyadarshini,
Dr. S. Panigrahi and
Dr. C. C. Rath**

**DARSHAN PUBLISHERS
TAMIL NADU, INDIA**

First published in India in 2021

This edition published by Darshan publishers

<http://www.darshanpublishers.com>

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ISBN: 978-81-954602-4-3

Price: Rs: 600.00



Published by:

Darshan Publishers,
8/173, Vengayapalayam, Kakkaveri, Rasipuram,
Namakkal, Tamil Nadu,
India – 637406.
www.darshanpublishers.com
E-mail: darshanpublishers12@gmail.com

Printed by:

Dhazh Computers (Graphic Designer)
No: 442- A, 10th East Cross Street,
Munthirithoppu, Annanagar,
Madurai – 20, Tamil Nadu, India.
E-mail: narennarayanasamy@gmail.com

Editor's Message

Microorganisms are unseen, tiny organisms, ubiquitous in nature, commonly found in soil water air as hospitable environments and unhospitable environments where generally life is not thinkable like, boiling sulfur springs, hydrothermal vents, dead volcanos, salt pans, mono-soda lakes etc. These microorganisms growing in such unhospitable extreme environments are called as extremophiles. Studies on extremophiles, reveals the mechanism of their adaptation to such environments. And another warranted property is that, the enzyme system is capable of working, and the DNA is capable of replication in such harsh conditions as a matter of fact extremophiles survive, grow and multiply in these environments. The enzymes of extremophilic origin are called as extremozymes that find numerous applications in different industries and R & D activities for value added products. Just to quote one example it can be told that *Taq* polymerase, from the thermophilic bacteria *Thermus aquaticus* completely revolutionized the field of genetic research or in other words without *Taq* polymerase PCR would have not enjoyed the beauty it has today.

Endophytes are a group of microorganisms (fungi or bacteria), of unusual habitat, which colonizes the internal plant tissues (intercellularly and/or intracellularly) at some part of its life cycle, without causing any possible negative effect to the host plant. Endophytes generally the soil microorganisms shelter in the plant tissues due to environmental stress and/or microbial competitions. Generally the host provides nutrients and shelter in turn the endophytes result in growth promotion of the host plant. Endophytes result in plant growth promotion through plant growth hormone productions, siderophore productions, nitrogen fixations, phosphate and sulphate solubilization etc. In addition, they also produce secondary metabolites in the plant tissue that protects the host from pathogens. Endophytic microorganisms are isolated from a variety of plants and different parts are reported with antibacterial, antifungal, antiviral, anticancerous, antioxidant properties too. Many are reported to grow in extreme environments with bioremediation, biotransformation and bioaugmentation activities. Above facts indicates that there is a dire need of exploring endophytic microorganisms in order to tap their biotechnological potential for production of value added products for humans and to find their applications in different R & D activities.

The Compilation entitled “Endophytes: the Novel Microorganisms for Plant Growth Promotion” is a maiden effort carried out by the authors to compile endophytic research carried out by different researchers throughout the globe. The compilation will help the academicians, researchers, scientists, especially working in the area of endophytic research for understanding the molecular mechanism of adaptation of the endophytes, in the unique ecological niche, as well as tapping the potential of these microorganisms for sustainability of the ecosystem and human society.

THE EDITORS

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Volume -1 Edition-1-2021

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Endophytic Fungi and Their Importance

N. Kistu Singh

Research Scholar, Department of Botany, Manipur University,
Canchipur – 795003, Manipur

E-mail: nkistusingh@gmail.com

Introduction

Microorganisms such as bacteria, fungi, archaea, algae, and protists are found both inside and outside of plant tissues. Mycorrhizal and endophytic symbiotic relationships with plants are the most prevalent, and their affiliation benefits the plant's growth, development, and disease resistance (Khare *et al.*, 2018). Endophytic fungi are those that live within photosynthetic plant tissue and have a symbiotic relationship with the host plant, causing no harm to it (Arnold *et al.*, 2000). They dwell within the intercellular gaps of the interior plant tissues underneath the epidermal cell layers. The researchers became interested in endophytic fungi after discovering the anticancer medication taxol from *Taxomyces andrenae*, which was derived from *Taxus brevifolia*, a Pacific yew tree (Heinig *et al.* 2013). Endophytic fungi have been isolated from a variety of hosts, including bryophytes and angiosperms, and have been cultivated in a variety of environments, from xeric to arctic, temperate to tropical woods, grasslands to croplands, and savannahs, but those derived from medicinal plants are becoming increasingly popular for agricultural, industrial, medical, and pharmaceutical uses for antibacterial, anticancer, anti-inflammatory, and other bioactivities (Jia *et al.*, 2016). It is believed that approximately 80% of the world's population uses plants as therapeutic resources, suggesting the most important alternative in developing countries would be endophytic fungi (Shakya, 2016).

The solubilisation of phosphorus, potassium, and zinc by endophytic fungus stimulates the growth of the hosts. They also protect them from pathogens through hyperparasitism, niche exclusion, competition, or antibiosis by producing extracellular enzymes such as pectinases, cellulases, lipases, amylases, laccases, xylanase, and proteases, or by activating plant defences; herbivory through direct exposure or the production of insecticidal compounds; altering plant hormone levels such as auxin, abscisic acid (Poveda *et al.*, 2021). Acidification, chelation, exchange reactions, and the release of organic acids are some of the methods used by endophytic fungi to mobilise plant

nutrients (Verma *et al.*, 2017). Endophytic fungi can become pathogenic under plant stress, and asymptomatic colonisation is thought to be the consequence of a balanced antagonistic interaction between plants and fungi; when this balance is disrupted, disease develops (Schulz & Boyle, 2005). Endophytic fungi have a complicated nature that has yet to be fully understood, necessitating more investigation.

As human civilization has advanced, the toxification of the environment has increased considerably. Metal bioremediation capability is shown by endophytic fungi isolated from plants cultivated in polluted locations with metals such as cadmium, lead, zinc, manganese, and cobalt (Krishnamurthy *et al.*, 2017). Plants that thrive in tropical or semitropical climates have a wider range of endophytes than those that grow in dry or cold climates. According to the World Health Organization (WHO), antimicrobial resistance (AMR) has emerged as one of the most pressing public health issues of the twenty-first century (Global Report on Surveillance of Antimicrobial Resistance, 2014). Nanoparticles have emerged as a novel antibacterial agent in the fight against antibiotic-resistant bacteria (Kim *et al.*, 2007). Silver nanoparticles are distinguished from other metal nanoparticles by their unique properties, which include chemical stability, conductivity, catalytic capabilities, and antibacterial potential across a wide variety of applications (Diantoro *et al.*, 2018).

According to studies, only 5% of the world's fungi have been found. Endophytic fungi are the least researched and characterised among the fungi, so they might produce new substances with broad applicability (Patil *et al.*, 2016). Endophytic fungi are being used biotechnologically to make biofertilizers and biopesticides, assuring long-term agricultural sustainability. Biological control is now universally accepted as a safe method for managing plant diseases and ensuring long-term agriculture. The biocontrol capability of several endophytes against various plant diseases has been studied. Natural and man-made factors such as drought, high temperatures, salt, and toxicity are putting a strain on crop production, particularly in tropical areas, resulting in yield losses of more than 50% globally. As a result of rapid climate change, abiotic stresses are expected to become increasingly widespread in the coming decades, posing serious threats to global food security (Nouh & Abdel-Azeem, 2020). Commercialization is still limited by attenuation, shelf life, regulation, and variations between laboratory and field results, despite the fact that endophytic fungi can be cultivated under controlled conditions (Latz *et al.*, 2018).

Isolation of endophytic fungi:

The endophytic fungi remain hidden within the healthy host tissues, so their symptoms and identifying characteristics, including the reproductive structures, are difficult to visualize. The isolation and diversity of endophytic fungi from plant components are affected by the surface sterilisation method. Thin, sensitive leaves need less time to sterilise than thick, hard leaves. The sampling size has a significant impact on the endophyte species richness, as a small sample size will overlook tiny mycocommunities (Mazaris, 2008). Endophytic fungi are tissue and organ specific, hence variation occurs within the leaves, inflorescence, stem, and roots of a given host (Nalini *et al.* 2014). The canopy level and the age of the tree are two more factors that impact species diversity and richness.

Isolation steps:

1. Before surface sterilisation, the plant samples must be rinsed in running tap water for 30 minutes to remove any surface adhesion and soil particles.
2. The plant components should be surface sterilised by passing them through a succession of sterilising chemicals. To remove the chemicals from the plant materials, first wash them twice in sterile distilled water, then immerse them in 70% ethanol for 2 minutes, 4% sodium hypochlorite (NaOCl) solution for 3 minutes, 70% ethanol for 30 seconds, and 70% ethanol for 30 seconds before washing them three times in sterile distilled water for one minute each.
3. The plant materials must be dried on the filter paper and cut to a size of 0.5 cm to 1 cm and aseptically transferred to PDA plates supplemented with Streptomycin sulphate (500 mg/L) to reduce bacterial growth. The plates should be incubated at $28\pm 1^{\circ}\text{C}$ for 5 to 7 days and checked regularly.
4. The fungal hyphal tips that emerged from the plant bits should be transferred into fresh PDA plates without antibiotics to make a pure culture and then incubated.

Commonly isolated endophytic fungi groups:

Porras–Alfaro *et al.* (2008) found that a single leaf in the tropics may harbour up to 90 endophytic fungal species, whereas grassland species can contain up to 50 genera. Endophytic colonisation rates in arctic and boreal ecosystems range from 1% to 44%, whereas colonisation rates in tropical habitats exceed 90%. (Higgins *et al.*, 2007). Molecular methods have been used to identify several of the endophytic fungi to species level. The majority of endophytic fungi are ascomycetes, which are ecologically diverse. The most prevalent endophytic fungi classes among ascomycetes are Sordariomycetes, Dothideomycetes, Eurotiomycetes, and Leotiomycetes, with prominent orders such as Pleosporales, Xylariales, Hypocreales, Eurotiales, Botryosphaeriales, and Sordariales (Wang *et al.*, 2016). In boreal, tropical, and arctic hosts, Dothideomycetes, Sordariomycetes, Leotiomycetes, Chaetothyriomycetidae, and Pezizomycetes were identified as important classes (Rungjindamai *et al.*, 2008). Even in polar plants, Ascomycota has been found to be prevalent. Agaricomycetes, Microbotryomycetes, and Tremellomycetes were found to be the dominating classes, while Agaricales, Polyporales, and Cantharellales were the main orders of Basidiomycota (Botnen *et al.*, 2014). In temperate regions, Sordariomycetes were found to be the most common fungi, followed by Dothideomycetes and Leotiomycetes (Arnold, 2008). Only a few isolates from Chytridiomycota, Mucoromycota, and Zygomycota are reported.

Growth and fitness promotion of host plants by endophytic fungi:

Endophytic fungi not only release hormones but also enhance hormones produced by the host plant, such as indole-3-acetic acid, indole-3-acetonitrile, and cytokinins, which help the host plant grow and thrive (Turbat *et al.*, 2020). Endophytic fungi have been proven to aid host development by regulating the expression of certain enzymes and proteins. Sánchez-Rodríguez *et al.* (2018) found that endophytic fungi that support plant development are predominantly Ascomycota, with a few belonging to Basidiomycota and Zygomycota (*Mucor*, *Rhizopus*). Endophytes could mobilise insoluble phosphate and supply nitrogen to their hosts by producing ammonia. When compared to crops without endophytes, agricultural crops with fungal endophytes provide better yields (Gond *et al.*, 2015). Endophytic fungi such as *Penicillium chrysogenum* and *Alternaria alternata* produce considerable quantities of IAA, which helps maize plants grow longer roots (Fouda *et al.*, 2015). Because of its high gibberellin activity, a pestalotin analogue isolated from *Pestalotiopsis microspora* improved the seed germination rate of *Distylium chinense* (Li *et al.*, 2015). Some endophytic fungi from *Cymbidium aloifolium* can produce

antibacterial siderophores which provide iron to the host plant (Chowdappa *et al.*, 2020).

Stress resistance of host plants by endophytic fungi:

Endophytic fungi produce a wide range of bioactive compounds that aid host plants in surviving biotic and abiotic stresses. They also activate the host plant's defence system. In several investigations, endophytic fungi produce bioactive compounds that have antibacterial properties against infections. Insects that attack host plants have been found to be harmful to the bioactive compounds (Hartley & Gange, 2009). A wide range of antioxidant compounds produced by endophytic fungi has been proven to enhance resistance to abiotic stresses. Reactive oxygen species (ROS) form inside plant tissues in response to environmental stresses such as heavy metal pollution, causing oxidative damage to proteins, nucleic acids, and membranes (Das & Roychoudhury, 2014). Endophytic fungi with metal sequestration mechanisms allow host plants to thrive in such soil.

Endophytic fungi against biotic stresses:

Pathogens such as fungi, bacteria, oomycetes, nematodes, and herbivores, as well as other pathogens, induce biotic stress in agricultural crops, resulting in significant economic losses. Endophytic fungi might help to resist such biotic pressures.

i. By producing antimicrobial compounds:

An antimicrobial compound is a chemical that may kill or limit the development of bacteria, fungi, and algae. Suppressing pathogen growth is one of the most important ways of improving plant health. Endophytic fungi increase the host plant's immunity against diseases by producing antimicrobial compounds. Four endophytic fungal isolates of *Aspergillus*, *Penicillium*, *Fusarium*, and *Phoma* from finger millet were able to produce anti-*Fusarium* compounds (Shikano *et al.*, 2017). *Phialocephala sphareoides*, a root endophyte identified from Norway spruce, generates antifungal chemicals that protect the host plant against diseases like *Heterobasidion parviporum* and *Phytophthora pini* that cause root rot (Terhonen *et al.*, 2016). Endophytes can operate as a component of plant defence in addition to producing antibacterial compounds. The c-di-GMP-dependent signalling pathway is required for endophytic signalling to take place (Mousa *et al.*, 2016). Endophytic fungi can also cause host plants to overproduce antibacterial or immunological compounds. *Trichoderma hamatum*, an endophytic fungus, has been found to

boost salicylic acid production and overexpression of defence enzymes and pathogenesis-related (PR) proteins (Siddaiah *et al.*, 2017).

ii. By producing extracellular enzymes:

Extracellular enzymes are enzymes that are released by a cell but function outside of it. These enzymes are generated by both prokaryotic and eukaryotic cells and have been shown to be important in a variety of biological activities. Humans have exploited many kinds of microbial exoenzymes for a variety of reasons dating back to prehistoric times, including food production, biofuels, textile manufacture, and the paper industry, as well as bioremediation of ecosystems. Endophytic fungi generate extracellular enzymes that hydrolyze plant cell walls. These enzymes can kill phytopathogens by damaging their cell membranes. Endophytic fungi like *Colletotrichum* sp., *Macrophomina phaseolina*, *Nigrospora sphaerica*, and *Fusarium solani* associated with *Catharanthus roseus* produce the enzyme cellulase (Ayob & Simarani, 2016). Enzyme production was found in forty endophytic fungal isolates from *Ocimum* species, including amylase, protease, and tyrosinase (Pavithra *et al.*, 2012). The endophytic fungus *Colletotrichum* sp. associated with soybean leaves is an essential endophytic fungus capable of producing enzymes during the final stage of leaf formation, and these enzymes aid in the breakdown of plant material (Fernandes *et al.*, 2015).

iii. By protecting host plant against herbivory:

Endophytic fungi can defend plants against herbivores by producing harmful compounds that prevent the animals from eating them. Several studies have found that entomopathogenic endophytic fungi have a negative impact on insect pests feeding on host plants. Reduced insect developmental rate, producing feeding deterrents, insect growth retardation, lowering survival rates, and oviposition are some of the mechanisms by which endophytic fungi limit insect herbivore damage. The endophytic fungus *Neotyphodium coenophialum*, isolated from *Festuca arundinacea*, causes toxicosis in calves that consume the plant because it produces bioactive compounds (White *et al.*, 2002). Phytohormones produced by certain endophytic fungi have been proven to boost the host plant's immune response against herbivores. *Epichloe* produces a range of alkaloids that protect the host plant against herbivores (Brem & Leuchtmann, 2001). *Periglandula*, an endophytic fungus identified from the morning glory family, has also been found to produce ergot alkaloids, making the plant very poisonous to herbivores (Leistner & Steiner, 2018). During herbivore stress, both harmful chemical defence mechanisms and plant

hormone defence systems were revealed to be linked as per recent meta-analysis (Bastias *et al.*, 2017).

i. By suppressing plant diseases through:

a) Induced resistance:

Induced resistance to diseases may be defined as “the process of active resistance dependent on the host plant’s physical or chemical barriers, activated by biotic or abiotic agents” (Kloepper *et al.*, 1992). Induced resistance is effective against viruses, bacteria, fungi, phytonematodes, and abiotic stressors, and it is also stable due to the participation of several resistance pathways, emphasising non-specificity, systemicity, and persistence. The inducing chemical leads the host to create a translocatable signal, which causes the host to respond in the future in a pathogen-resistant manner. In response to the plant signal, the inducing chemical causes changes in gene expression, protein synthesis, and metabolic alterations. These changes in plant metabolism decrease the plant's suitability as a host, resulting in a reduction in disease levels. The inducing agents might be living beings or chemical molecules, and the host's response can be local or systemic (Oostendorp *et al.*, 2001). The plant recognises both pathogen and endophytic fungal reactions, but their defence responses differ. Plant receptors recognise pathogen-associated molecular patterns (PAMPs) or microbe-associated molecular patterns (MAMPs), triggering PAMP/MAMP-triggered immunity. Chitin and glucans found in fungal cell walls are important MAMPs that plant receptors recognise (Lyon *et al.*, 2014). The two types of systemic resistance are "systemic acquired resistance" (SAR) and "induced systemic resistance" (ISR). SAR is influenced by the hormone salicylic acid (SA), whereas ISR is influenced by the hormones jasmonic acid (JA) and ethylene (ET) (Kamle *et al.*, 2020). This shows the complexity of hormonal interactions, and how introducing endophytic fungi to a plant changes the overall hormone balance.

b) Antibiosis:

Many endophytic fungi produce specialised metabolites and chemicals that can prevent other microorganisms from growing. To tackle phytopathogens, several researchers have been attempting to discover, isolate, and synthesise economically viable fungal metabolites. Recent research has revealed antimicrobial compounds from endophytic fungi, such as alkaloids, flavonoids, peptides, phenols, quinones, steroids, terpenoids, and polyketides (Lugtenberg *et al.*, 2016). In other instances, the host and endophyte share pathways and contribute to metabolite production in part, or one partner drives

the metabolism of the other. For example, the endophytic fungus *Neotyphodium lolii* extensively expressed the gene cluster for the alkaloid lolitrem when attached to cold-season grasses, but generated exceedingly weakly or at low levels in vitro (Young *et al.*, 2006). Endophytic fungi have been proven to produce disease-fighting compounds in vitro, although they may not do so while within the host plant (Mathivanan *et al.*, 2008). This might be due to a lack of nutrients, changing environmental conditions, or interactions with other organisms like pathogens and endophytes.

c) Mycoparasitism:

Mycoparasitism occurs when one fungus takes nutrition from another fungus, whether through a biotrophic or necrotrophic connection (Viterbo & Horwitz, 2010). Mycoparasitism research is often conducted in vitro rather than on plants, and direct interactions between the parasite and its two hosts may be studied using modern microscopy techniques. It has been shown to involve four sequential steps: chemotropism, recognition, attachment and coiling, and cell wall penetration and digestion of host cell content (Chet *et al.*, 1998). The mycoparasite establishes direct contact with the host hyphae, then enters, coils around, and kills the prey hyphae (Karlsson *et al.*, 2017). In the cytoplasm of eight soil-borne diseases, three endophytic fungi isolated from *Phragmites australis* were found (Cao *et al.*, 2009).

d) Competition:

Endophytic fungi have demonstrated that competition is a key strategy for preventing diseases from colonising the host plant. The fungal endophytes colonise different areas of the plant tissues in a local or systemic way, which may be intercellular or intracellular in nature, and scavenge the available resources, occupying a niche and leaving no room for harmful organisms (Boyle *et al.*, 2001). The removal of some endophytes from mango leaves through fungicide treatment creates space for possible diseases (Mohandoss & Suryanarayanan, 2009). Another study discovered that foliar application of isolated endophytes from cacao tree leaves to endophyte-free seedlings reduced disease caused by *Phytophthora* spp. foliage through a competitive mechanism (Arnold *et al.*, 2003). In addition, endophytic colonisation of tomato and cotton seeds by *Beauveria bassiana* can prevent seedling illnesses caused by *Rhizoctonia solani* and *Pythium myriotylum*, showing space competition (Ownley *et al.*, 2008).

Endophytic fungi against abiotic stresses:

Abiotic stress is the leading cause of crop loss, accounting for more than half of worldwide crop production (Yadav *et al.*, 2020). Plants undergo morphological, physiological, biochemical, and molecular changes as a result of abiotic stress, all of which have an influence on their growth and productivity. The discovery of fossilised fungal hyphae and spores has proven the importance of endophytic fungi in ancient terrestrial plant survival against abiotic stressors such as drought, salt, metal, UV radiation, and temperature changes (Venugopalan & Srivastava, 2015). Abiotic stresses impair the genetic regulation of cellular processes, resulting in the accumulation of reactive oxygen species (ROS), membrane dysfunction, and hormonal imbalance, all of which affect the plant's morphology and physiology.

i. Resistance to salinity stress:

Salinity has harmed more than 45 million hectares of irrigated land worldwide, with 1.5 million hectares lost to production each year as a result of excessive salt levels in the soil. Salinity has influenced plant development, such as germination, vegetative growth, and reproductive development (Shrivastava & Kumar, 2015). As a result of soil salinity, which hinders water mineral absorption, plants are subjected to ion toxicity, osmotic stress, nutritional (N, K, P, Ca, Fe, Zn) deficiencies, and oxidative stress (Arif *et al.*, 2020). Plants are vulnerable to ionic stress when they are exposed to salt for an extended length of time, which can result in the premature senescence of adult leaves, lowering the amount of photosynthetic surface available to support continued development. Plant resistance to salt stress is related to the loss of antioxidant enzymes. Salt tolerance is induced in barley by the endophytic fungi *Piriformospora indica*, which increases antioxidant levels (Baltruschat *et al.*, 2008).

ii. Resistance to drought stress:

Drought is a major determinant of agricultural productivity across the world, and its frequency is expected to increase year after year due to climate change. The production of phytohormones by endophytic fungus has the potential to increase plant drought tolerance (Khan *et al.*, 2013). Plants have been demonstrated to be protected against oxidative damage by activating stress-sensitive genes and strengthening the antioxidant system. Drought stress is being treated with exogenous ABA treatment. In addition to ABA, exogenous salicylic acid (SA) may also aid in mitigating the negative consequences of drought stress (Silva *et al.*, 2017). Plants also produce a

number of secondary metabolites that help in drought stress management. Drought reduces photosynthesis and protein synthesis, increases photorespiration, disrupts cell homeostasis, alters plant hormone balance, and raises reactive oxygen species (ROS) levels in plant cells. Drought stress lowers water-soluble nutrient diffusion and mass flow, such as nitrate, sulphate, calcium, magnesium, and silicon (Selvakumar *et al.*, 2012).

iii. Resistance to heavy metal stress:

Heavy metal stress has emerged as a serious problem in a variety of terrestrial ecosystems across the world. Modern industrialisation has a negative impact on soil and agricultural yield due to the accumulation of heavy metals. Among heavy metals, the most hazardous metals are As, Pb, Cd, and Hg (Pandey & Madhuri, 2014). Earlier studies suggest that plant endophytic fungi have a high level of metal tolerance and healing capabilities in contaminated soils. *Exophiala pisciphila*, a root-associated endophytic fungus of *Zea mays*, has a strong resistance to Cd, resulting in a significant reduction in Cd phytotoxicity and an increase in maize growth (Wang *et al.*, 2016). Endophyte phytohormones improve plant tolerance to heavy metal stresses. Fässler *et al.* (2010) discovered that IAA supplementation reduced the negative effects of lead on sunflower growth by increasing root volume, surface area, and diameter. SA signalling has also been found to generate a hypersensitive response, which is followed by the formation of "systemic acquired resistance," which relieves heavy metal stress.

Bioactive compounds from endophytic fungi:

Chemical compounds that have biological impacts on living organisms are referred to as bioactive substances. Many endophytic fungi have the ability to increase the accumulation of secondary metabolites from host plants, thus affecting the quantity and quality of pharmaceuticals. These compounds usually have antibacterial, antifungal, immunosuppressive, antiviral, antiparasitic, antioxidant, anticancer, or antitubercular bioactivities (Singh *et al.*, 2021).

i. Bioactive Compounds as Antibacterial Agents:

According to the World Health Organization (WHO), antibiotic resistance is one of the most serious threats to human health, and it puts a huge financial strain on healthcare systems across the world (Aslam *et al.*, 2018). Endophytes have been proven in various investigations to have secondary chemical resistance mechanisms to counteract pathogenic invasion.

Antibacterial compounds generated by endophytes have been identified as alkaloids, peptides, steroids, terpenoids, phenols, quinines, and flavonoids (Burraroni & Jeon, 2021). Secondary metabolites of *Aspergillus niger*, *Curvularia pallescens*, *Guignardia bidwelii*, *Paecilomyces variotii*, and *Mycelia sterilia* have been found to have antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Enterococcus faecalis*, *Micrococcus luteus*, *Escherichia coli*, and *Pseudomonas aeruginosa* (Silva *et al.*, 2011). *Penicillium janthinellum*, an endophytic fungus isolated from the fruits of *Melia azedarach*, produced the polyketide citrinin, which demonstrated 100% antibacterial effectiveness against *Leishmania* sp. (Momose *et al.*, 2000).

ii. Bioactive Compounds as Antifungal Agents:

In the agricultural sector, fungal infections cause crop damage, economic losses, and, ultimately, food security and food production. Furthermore, microorganism resistance to currently available antimicrobials, notably antifungal medications, has increased. Pathogenic fungi are opportunistic and infect immunocompromised people, putting a burden on current global health-care systems. In patients infected with the Covid-19 virus in South Asian countries, mucormycosis (black fungus infection) has been recorded (Rahman *et al.*, 2021). Several fungal metabolites from the endophytic fungus *Aspergillus fumigatus*, such as 12-hydroxy-13-methoxyverruculogen TR-2, fumitremorgin B, verruculogen, and helvolic acid, as well as others, demonstrated substantial antifungal activity against a range of phytopathogenic fungi (Li *et al.*, 2012). *Cladosporium cladosporioides* and *Cladosporium phaeospermum* were resistant to five cadinanesesquiterpenoids isolated from the endophytic fungus *Phomopsis cassiae* and obtained from *Cassia spectabilis* (Silva *et al.*, 2006).

iii. Bioactive Compounds as anticancer agent:

According to the report (Bray *et al.*, 2018), cancer is the world's second leading cause of death. Lung, prostate, colorectal, stomach, and liver cancer are more common in men, whereas breast, colorectal, lung, cervical, and thyroid cancer are more common in women (Jung *et al.*, 2018). Furthermore, cancer patients usually have unfavourable side effects as a result of therapeutic techniques, which are also associated with significant toxicity. The endophyte *Chaetomium globosum* of the *Ginkgo biloba* plant produces three novel compounds: azaphilone alkaloids, chaetomugilides A–C, and chaetoviridin E, which all exhibit high cytotoxic action against the human cancer cell line HePG2 (Li *et al.*, 2013). Endophytic fungi including *Fusarium oxysporum*,

Aspergillus fumigatus, *Phialocephala fortinii*, and *Trametes hirsute*, as well as *Trichoderma*, *Penicillium*, and *Phomopsis* species, have been found to produce podophyllotoxin, which possesses anticancer effects (Manganyi & Ateba, 2020). Extracts from endophytes, *Fusarium* sp., and *Aspergillus fumigatus* inhibited HeLa cervical cancer cell lines (Ruma *et al.*, 2013).

iv. Bioactive compounds as antioxidant Agent:

Free radicals are highly unstable molecules that develop spontaneously as a result of chemical reactions such as digestion. These free radicals have the potential to start chain reactions in the human body, which might result in cell damage. Numerous studies have revealed that oxidative stress is linked to cellular degeneration, cancer, atherosclerosis, coronary heart disease, diabetes, Alzheimer's disease, hepatic and renal damage, and other neurological disorders (Rahman *et al.*, 2012). Antioxidant chemicals are used to treat, prevent, and cure diseases and injuries caused by reactive oxygen species (ROS) (Battin & Brumaghim, 2009). Free radical scavenging chemicals such as phenolic compounds, nitrogen compounds, vitamins, terpenoids, and other endogenous metabolites are abundant in medicinal plants. However, due to over-harvesting, illegal exploitation, and destruction of ecological habitat, medicinal plant resources are rapidly diminishing, necessitating the conservation of endangered medicinal plants as well as the development of new alternative sources for developing antioxidants from plants. These medicinal plant endophytes might be a good source of antioxidants. The endophyte *Xylaria* sp. from the medicinal plant *Ginkgo biloba* produced a total of forty-one bioactive compounds with antibacterial, antioxidant, anti-cardiovascular, anticancer, and antimicrobial properties (Manganyi & Ateba, 2020). Pestacin, isopestacin, and 1, 3-dihydro isobenzofurans were revealed to exhibit significant antioxidant activities in the endophytic fungus *Pestalotiopsis microspora* harboured in *Terminalia morobensis* (Zhou *et al.*, 2018).

v. Bioactive compounds antiparasitic agents:

Approximately 48.4 million individuals are infected with parasites each year, resulting in one million deaths (Torgerson *et al.*, 2015). Despite this, there are currently only a few very effective antiparasitic drugs available. *Diaporthe phaseolorum*, an endophytic fungus isolated in the roots of *Combretum lanceolatum*, inhibited *Trypanosoma cruzi* amastigotes and trypomastigotes by up to 82 percent (Azevedo *et al.*, 2021). Another study discovered that Oxylipin (9Z,11E)-13-oxooctadeca-9,11-dienoic acid extracted from the endophytic fungus *Penicillium herquei* was efficient against

Plasmodium falciparum, *Trypanosoma brucei*, *Leishmania donovani*, and *Leishmania* sp. (Hayiboret *et al.*, 2019).

vi. Bioactive compounds as Immunosuppressive Drugs:

Anti-rejection medications are immunosuppressive medicines that are used to reduce, minimise, or prevent allograft rejection in individuals who have had an organ transplant. The efficiency of immunosuppressive drugs is currently being limited by a number of side effects, and owing to their high demand, discovering safer, more effective treatment is necessary. Recent research has discovered that endophytes create bioactive chemicals with immunosuppressive effects (Manganyi&Ateba, 2020). Recently discovered immunosuppressive therapies from fungal endophytes include sydoxanthone A and B, colutellin A, 13-O-acetylsydowinin B, dibenzofurane, methyl peniphenone, xanthone derivatives, subglutinin A and B, lipopeptide, peniphenone, benzophenone derivatives, (-) mycousnine, polyketide benzannul (Adeleke & Babalola, 2021).

vii. Bioactive compounds as antiviral agent:

Viruses are entities that replicate only within live cells and are a major cause of mortality and illness in humans all over the world. Ideal antiviral drugs should be efficient against the target virus strains while causing little harm to the host cells. Antiviral chemicals found in the endophytic fungus *Emericella* sp. from the mangrove plant *Aegiceras corniculatum* include emerimidines A and B, emeriphenolicins A and D, as well as aspernidines A and B, austin, austinol, dehydroaustin, and acetoxyldehydroaustin (Zhang *et al.*, 2011). Endophytic fungi isolated from Egyptian medicinal plants have recently been found to have potent antiviral activity against herpes simplex virus (HSV-2) and vesicular stomatitis viruses (VSV) (Selim *et al.*, 2018). Endophytic fungi found in the leaves of *Quercus coccifera* have been shown to produce the antiviral compound Hinnuliquinone, which is a potent inhibitor of the HIV-1 protease (Singh *et al.*, 2004).

viii. Bioactive compounds as antitubercular agent:

The World Health Organization (WHO) estimates that 50 million people are afflicted with TB globally, with 1500 people dying every hour. Following the advent and spread of drug-resistant *Mycobacterium* TB strains, the quest for novel anti-mycobacterial medicines has started. Medicinal plants have long been known as a source of fungal endophytes with new molecular structures and physiologically active chemicals that can be used to treat a

variety of human pathogenic illnesses. Phomoxanthone A and B, which have substantial anti-*M. tuberculosis* action, were isolated from the endophytic fungus *Phomopsis* sp. of *Garcinia* sp. (Phongpaichit *et al.*, 2007). *Phomopsis* sp. isolated from *Garcinia dulcis*, was also shown to generate metabolites that inhibit *M. tuberculosis*, such as Phomoenamide and Phomonitroester. Tenuazonic acid was extracted from the endophyte *Alternaria alternata* and it was found to be potent against *M. tuberculosis*. *Diaporthe* sp., isolated from *Pandanus amaryllifolius* leaves, developed diaportheone A and B, two novel benzopyrans that limit the development of aggressive *M. tuberculosis* strains (Bungihan *et al.*, 2011).

Role of endophytic fungi in bioremediation:

Bioremediation can be defined as any process that uses bacteria, fungi, green plants or their enzymes to return the environment altered by contaminants to its original condition. Microorganisms, particularly endophytes, have the ability to bioaccumulate heavy metals and other contaminants from the environment, as well as enhance plant growth by mobilising and immobilising toxins. *Neotyphodium* improves Cadmium tolerance in two plant species, *Festuca arundinacea* and *Festuca pratensis*, as compared to non-endophyte infected plants (Soleimani *et al.*, 2010). *Penicillium funiculosum*, a fungal endophyte that shields plants from copper stress and stimulates plant development, can be used in cultivated areas for bioremediation (Khan & Lee, 2013). Mercury is a toxic metal that is highly mobile and persistent in soil, bioaccumulates and biomagnifies via the food chain, and poses a direct threat to human and animal health (Cozzolino *et al.*, 2016). Mercury has been released and accumulated in many ecosystems due to human activities like illegal gold mining (Obrist *et al.*, 2018). High amounts of mercury impair plant growth at all stages, decreasing seed germination and water absorption, lowering biomass, denaturing proteins, and impeding photosynthesis (Patra & Sharma, 2000). In this regard, inoculating plants with mercury-resistant endophytic fungus might help increase mercury phytoremediation performance. *Pestalotiopsis microspora*, an endophytic fungus, has been found to thrive in both aerobic and anaerobic conditions using the synthetic polymer polyester polyurethane as the only carbon source, meaning that it might be used to treat white plastic pollution (Russell *et al.*, 2011).

Bioprospecting potential of endophytic fungi:

Bioprospecting is the study of plants, animals, and microbes in order to find active ingredients that may be used in biotechnology. Endophytic fungi are a significant source of bioactive chemicals and may be used for a variety of bioprospecting applications (Soares *et al.*, 2017). Some of the substances produced by endophytes that have antagonistic activity are aliphatic compounds, phenolic compounds (phenols and phenolic acids), isocoumarin derivatives, lignans, flavonoids, and quinones), alkaloids (indole derivatives, amines, and amides), peptides, polyketides, steroids, and terpenoids (primarily sesquiterpenes, diterpenes, and triterpenes). Endophytic fungi have been the subject of studies aimed at identifying novel bioactive natural compounds that might be used in pharmaceuticals, food, and agriculture.

Endophytic fungi produce extracellular enzymes that are important in industry. Protease is used in a broad range of sectors, including biscuit manufacture, brewing, and photography. Proteases are employed in therapeutic applications, particularly in diabetes therapies. Lipases are enzymes that catalyse the hydrolysis of triglycerides with long chains. The range of industries and applications covered by industrial lipases includes oleochemicals, detergents, polymers, food processing, pharmaceuticals, trash, cosmetics, and biodiesel. The Amylase enzyme can be used in many industries, including food, fermentation, textiles, paper, detergents, pharmaceuticals, and sugar. Microbial enzymes are better adapted to industrial needs since they are less expensive to generate and are more predictable, controllable, and dependable. Souza & Magalhes (2010) define the genus *Mucor* as a group of fungi that produce amylases, which are frequently employed in industry. In terms of production, cellulases are the third most industrially significant enzymes worldwide. They are used in cotton processing, paper recycling, juice extraction, enzymatic detergents, and animal food additives. Laccases enzyme has the ability to oxidise both phenolic and non-phenolic aromatic chemicals, which has piqued the interest of researchers in the food, pulping, textiles, wastewater treatment, and bioremediation industries. Laccase can also be used in biosensors, enzymatic assays, and immunochemical tests for analytical purposes. Xylanases are extracellular enzymes generated mostly by fungus that may be used to bleach kraft pulp in the paper industry. Endophytic fungi have also been associated with environmental recovery, such as the recycling of agricultural and agro-industrial waste and the biodegradation of lignocellulosic materials, such as wood. Oxidative enzymes, particularly laccase and peroxidase enzymes, generally catalyse these breakdown processes.

Endophytic fungi benefit host plant physiology, and their capacity to produce enzymes may impact litter decomposition, nitrogen cycling, and nutrient intake by hosts (Pragathi *et al.*, 2013).

Until recently, crop spraying with a range of synthetic chemical pesticides was the primary method of pest, disease, and weed management. Because of the growing agricultural necessity to sustain population growth, this strategy increased the use of toxic and carcinogenic chemicals, putting the plant's and consumers' health in jeopardy. Another application for fungus-derived chemicals in agriculture is biological control, which provides a long-term alternative to chemical control. Several *Trichoderma* species are among the most studied fungal endophytes. *Trichoderma* spp. has parasitized *Sclerotium sclerotiorum* and *Rhizoctonia solani* hyphae, for example (Melo & Faull, 2000). Webber was perhaps the first to mention using an endophytic fungus for biological control (Webber, 1981). *Metarhizium anisopliae* and *Beauveria bassiana*, two insect pest controls, are now often used in agriculture (Sinia & Guzman-Novoa, 2018). *Muscador vitigenus*, a fungal endophyte isolated from *Paullinia paullinioides* Radlk., generates the insect repellent naphthalene (Strobel *et al.*, 2002). Fungal endophyte species have been discovered to synthesise metal, silver, copper, zinc, magnesium, and gold nanoparticles (Messaoudi & Bendahou, 2020). Endophytic fungi-produced iron oxide nanoparticles have been reported to remove colours from textile and paper industry effluent without causing environmental harm (Samsami *et al.*, 2020). In addition, gold nanoparticles are non-toxic and absorb well, making them suitable for a number of medical applications (Valsalam *et al.*, 2019). *Fusarium solani*, an endophytic fungus, has been isolated from the plant *Chonemorpha fragrans*, which is used to make gold nanoparticles (Clarance *et al.*, 2020). Many researchers claim that gold nanoparticles are a good source of biosensors and cancer-killing agents (Arokiyaraj *et al.*, 2015).

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Access this Chapter in Online	
	Subject: Endophytic fungi
Quick Response Code	
DOI: 10.22192/enmpgp.2021	

How to cite this Chapter:

N. Kistu Singh. (2021). Endophytic Fungi and Their Importance. Sonali Priyadarshini, S. Panigrahi and C. C. Rath. (Eds), Endophytes: Novel Microorganisms for Plant Growth Promotion. India: Darshan Publishers. pp: 1-28.

Role and significance of endophytic fungi in crop improvement for sustainable agriculture: Current perspective and future trend

Kuntal Das¹; R.K.S. Tiwari²; Sumana Das³

¹Research Breeding Innovation Platform, International Rice Research Institute, South Asia Regional Centre, Varanasi, Uttar Pradesh 221106

²Department of Plant Pathology, B.T.C. College of Agriculture & Research Centre, Bilaspur, Chhattisgarh 495001

³Department of Botany, C.M. D. Postgraduate College, Bilaspur, Chhattisgarh, 495001

Corresponding Author: Dr. Kuntal Das

E-mail: kdas_mail@yahoo.com; k.das@irri.org

Abstract

Endophytes are non-disease causing microbes (bacteria and fungi) surviving in living tissues of plants. Endophytic fungi play a key role in habitat adaptation of plants resulting in improved plant performance and ensuring protection against biotic and abiotic stresses and in nutrient acquisition. Fungal endophytes confer profound impacts on their host plants by enhancing their growth, increasing their fitness, strengthening their tolerances to external stresses. Moreover, fungal endophytes symbiotic with host plant produce a plethora of bioactive secondary metabolites that are expressed as defensive weapons to protect the host plant. The last couple of decades have witnessed a burgeoning literature on the role of fungal endophytes in regulating plant growth and development and their adaptation to abiotic and biotic stresses. Several studies have raised the hope of their potential application in agriculture, especially in mitigating abiotic and biotic stresses in major crops. Here, we reflect on this paucity and elaborate on some of the important bottlenecks that might stand in way of fully realizing the potential on what fungal endophytes hold for crop improvement. We stressed on the need to study various facets of the endophyte-plant association for their gainful application in agriculture. The present review article describes the significant role and significant standpoint of endophytic fungi for sustainable agriculture.

Keyword: Endophyte, Fungi, Secondary metabolites, Sustainable agriculture, Crop improvements.

Introduction

Since time immemorial the association between plants and fungi is extremely common. Existing fossil records for more than 400 million years old indicate the presence of the union of endophytes and mycorrhizas with plants (Kringset al., 2007; Chadha et al., 2015) and started when plants colonized the soil, which indicate the importance of this group in the evolution of this process (Rodriguez et al., 2009). Two hypothesis which explains the origin of endophytes are validly exists namely exogenous and endogenous. According to exogenous hypothesis, the endophytes are believed to be arrive from outside of the plant and got inserted into the host from wound, induced channels, or tissue surfaces (Li, 2005), whereas exogenous hypothesis explains that the endophytes are gaged from the mitochondria and chloroplast of the plant and thus having comparable genetic background of the host plant (Wen, 2004). Generally endophytic fungi reside within plants and causing no harm on their growth and development. Endophytes are non-pathogenic and many of them are known to enhance their plant host's fitness (Mendes et al., 2013; Philippot et al., 2013). The positive aspects of plant and fungal endophyte interaction have always been noted and discussed, but detailed studies on the real significance of these fungal group have only been assessed recently (Busby et al., 2016; Card et al., 2016; Vega 2018; Quesada-Moraga 2020). Fungal endophytes exhibit a range of symbiotic relationships with their hosts and some of these interactions can be mutualistic in which the long-term relationship is beneficial to both partners (Card et al., 2016). The endophytic interaction is defined as balanced antagonism (Schulz et al., 2015) because the recognition of the plant as a host requires the activation of virulence mechanisms for colonization and the triggering of host defenses by these events.

Various aspects of the fungal endophytic interaction in crop improvement still needs to be fully elucidated, and research is undergoing to strengthen this understanding (Aly et al., 2011; Chadha et al., 2015; Khan et al., 2015). Awareness about the need for more sustainable agriculture is the main incentive for the recent scientific research and improving sustainable agriculture will help to protect and reduce the negative impacts on the environment in future (Jaber and Enkerli 2017; Baron et al., 2020). Among many attributes of endophytes, in particular their universal occurrence, sustained presence in plants, non-pathogenic nature, ability to enhance the

biotic and abiotic stress tolerance of their plant hosts (Rodriguez et al., 2009; Das et al., 2011), increase access to soil nutrients and increase the plant yield (White et al., 2019; Xia et al., 2019) project them as potential candidates in holding high promise for their extensive use in crop improvement.

Imprudent application of crop protection chemicals and fertilizers affecting the environment and human health. Residues from these chemicals can be found in foods, such as vegetables, fruits, cereals, and grains, and even byproducts such as juices and wines, depending on the practices adopted for their production (Zikankuba et al., 2019). Several studies indicate the occurrence of various human health disorders in children, adults and the elderly by exposure to pesticides, including Hodgkin's disease, lymphoma, Parkinson's disease, endocrine disorders, respiratory and reproductive problems in addition to cancer (Sabarwal et al., 2018). In addition, nontarget organisms are constantly being affected in the ecosystem and environment (Van Lexmond et al., 2015). The excessive use of chemical fertilizers leads to the accumulation of heavy metals, eutrophication of rivers and lakes, the acidification of soils, contamination of aquifers and water reservoirs, and generation of gases associated with the greenhouse effect (Savci, 2012; Kulkarni and Goswami, 2019). Underlying the knowledge about the symbiotic relationship between plants and soil microbiota along with the synergistic mode of action representing a positive interaction which is proven to be fundamental in search for alternative processes that could be employed to reduce or even replace the application of chemicals to develop make agriculture more sustainable (Carneiro et al., 2015; Ahmad et al., 2018). From this perspective, studies are focusing on characterizing endophytic fungal community of several plant species, especially those of agronomic interest. Several reports have shown that endophytic fungi plants by direct interactions where, the fungi are able to act as antagonists of plant pathogens using a diverse range of mechanisms, such as the production of metabolites (antibiotics, volatile compounds and enzymes), engagement in competition (for space, carbon sources, nitrogen and minerals) and parasitism. This causes the induction of systemic resistance by the plant and increases in plant growth, resulting in the reduction of the activity of the pathogens (Vega et al., 2009; Vidal and Jaber 2015; Vega 2018; Lr, 2018; Quesada-Moraga, 2020). The characterisation of endophytic fungi also expands the possibility of their use not only as biocontrol agents but also as biostimulants and biofertilizers in agriculture. After introducing some basic aspects of fungal endophytes, the primary aim of this paper is to provide insights on aspects of the scientific research depicting the potential role and significance of endophytic organisms

for crop improvement and commercialization as bioproducts for agriculture. We also reflect upon the gap and identify potential bottlenecks that might hinder the exploitation of endophytes in agricultural applications as well as discussed, the possible approaches that might help to pave the way ahead in allowing a gainful application of fungal endophytes in sustainable agriculture.

A. Fungal endophytes: What? Who? Where? How?

1. What are fungal endophytes?

The term ‘endophyte’ is derived from two Greek words: ‘endo’ or ‘endon’ meaning within, and phyte’ or ‘phyton’ meaning plant, as was first contrived by de Bary (1866) and denote all those microbes residing inside the living healthy plants (Kusari and Spiteller, 2012; Lata et al., 2018; Chhipa and Deshmukh, 2019). Leveillé recognized the fungi in wheat leaves and called them as endophytic fungi (Lata et al., 2018). Hallmann et al., (1997), defined as ‘those microorganisms that can be isolated from surface-disinfected plant tissue or extracted from within the plant, and that do not visibly harm the plant’. However, the definition is modified in recent years and endophytic fungi are considered as micro-fungi that internally infect living plant tissues without causing any symptomatic harm (disease) to plant, and live in mutualistic association with plants for at least a part of their life cycle (Kusari and Spiteller, 2012; Anitha et al., 2013; Lugtenberg et al., 2016; Arora and Ramawat, 2017; Jain and Pundir, 2017; Lata et al., 2018; Khare et al., 2018; Chhipa and Deshmukh, 2019, Hyde and Soyong, 2008; Rodriguez et al., 2009; Hardoim et al., 2015).). The scientific community now generally agrees that endophytes are microorganisms that can be detected inside healthy plant tissues and are asymptomatic. Fungal endophytes exhibit a range of symbiotic relationships with their hosts as well as various lifestyles in which the mutualistic long-term relationship is beneficial to both partners (Card et al., 2016). A more recent definition proposed by Le Cocq et al., (2017) concludes that endophytes are microbes which inhabit internal plant tissues for at least part of their life cycles and cause no harm to the host plant under any circumstance, meaning that those microbes currently considered as endophytes but which present harmful effect to a plant host at any moment should have their designation changed.

2. Who are fungal endophytes?

Fungal endophytes are classified into different functional groups based on various criteria is a useful framework for clarifying the unique symbiotic and ecological and fundamental biological role. Rodriguez et al., (2009)

described different functional groups of endophytic fungi based on their phylogeny and life history traits (Table 1).

Table 1. Endophytic fungi classes and their characteristics according to Rodriguez et al., (2009)

Class of endophytes	Main fungal genera	Common host/colonised tissues	Transmission	Reference
Class 1	Epichloë, Metarhizium, Claviceps and others	Grasses /shoot and roots	Horizontally and vertically	Faeth and Saari (2012) Behie and Bidochka (2014)
Class 2	Phylum Ascomycota Penicillium, Aspergillus, Fusarium, Colletotrichum, Trichoderma, Beauveria, Purpureocillium, and others Phylum Basidiomycota Xylaria spp.	Great host range/ roots, stem and leaves	Horizontally and vertically	Rodriguez et al., (2009) Hirumaet al., (2018) Waqas et al., (2012) Khan et al., (2008) Dash et al., (2018) Lopez and Sword (2015)
Class 3	Sobreposition with Class 2 endophytes in many cases. It depends on the host, local of infection in the plant and mode of transmission	Mainly tropical trees/ leaves	Horizontally only	Rodriguez et al., (2009)
Class 4	Curvularia, Alternaria, Phialocephala, Deschlera, Ophiosphaerella, Cladosporium, and others	Great host range/ Roots	Horizontally only	Rodriguez et al., (2009) Hamayunet al., (2010) Spagnolettiet al., (2017)

Bamisile et al., (2018) gathered information from several studies and proposed that endophytic fungi can be classified according their ecology, diversity and function. They can be classified as sexual or asexual according to the mode of reproduction by sexual or asexual spores. Additionally, they are horizontally or vertically transmitted based on their mode of transmission (Gimenez et al., 2007; Aly et al., 2011; Lugtenberg et al., 2016).

Endophytic fungi are divided into clavicipitaceous (usually associated with grasses) and non-clavicipitaceous (not found in grasses) (Hyde and Soyong, 2008). Class 1 endophytes are defined as the Clavicipitaceous endophytes (including *Balansia* spp. and *Epichloe* spp.) that are specific colonizers of grasses, and they can be found in the aerial part and/or roots of their hosts and are transmitted horizontally and vertically. The non-clavicipitaceous types are further separated into three subclasses, classes 2, 3 and 4. The diverse class 2 endophytes encompass both Ascomycota and a few Basidiomycota which are most distinctive as their ability to colonize roots, stems and leaves and the formation of extensive plant infections (Rodriguez et al., 2009). Endophytes from class 3 are extremely diverse and form highly localized infections in aboveground tissues, such as in the leaves of tropical trees and non-vascular and vascular plants (Rodriguez et al., 2009). Class 4 includes so-called dark septate endophytes, fungi that have melanin in their septa and occur exclusively in the roots of their hosts and present only horizontal transmission. (Rodriguez et al., 2009) and these facultative biotrophic fungi colonize plant roots and have the distinguishing feature of having melanized dark septate hyphae (Jumpponen and Trappe, 1998; Jumpponen, 2001). Finally, Recently, Lugtenberg et al., (2016) suggested the inclusion of an additional class for endophytic entomopathogenic fungi because they are able to grow as symptomless endophytes of several plant species and present the unique ability to infect and colonize insects.

3. Where are fungal endophytes?

In relation to their occurrence endophytic fungi have already been recovered from a wide range of habitats, including arctic environments, hot deserts, and mangrove, temperate and tropical forests (Arnold and Lutzoni, 2007; Arnold, 2008, Das et al, 2011). As reviewed by Chadha et al., (2015) and Lugtenberg et al., (2016). The characterization of the diversity and the distribution of fungal endophytes across large geographical areas is still in the initial phase, and only some general aspects can be affirmed, such as that the diversity of endophytic fungi is higher in the tropics than in higher

latitudes. Additionally, a higher number of endophytic species are found in tropical environments and belong to a small number of classes.

Diversity of endophytic fungi associated with plants can greatly vary according to environmental conditions (Vega et al., 2010), *i.e.*, even for plants of the same species, the assemblage of fungal endophytes inside their tissues can vary if the physiological state of each individual is different (Aly et al., 2011). Moreover, the age of the plant can also influence the fungal endophytic community profile (Sieber, 2007). Some fungal endophytes are able to colonize a wide range of plant species, while others are more specific and occur only inside a restricted number of plants. Additionally, specificity can also be present in relation to the portion of the plant that is colonized (Aly et al., 2011; Bamisile et al., 2018). Apparently, vertically transmitted fungi seem to present plant associations with a more mutualistic profile than horizontally transmitted fungi, which are more likely antagonists (Aly et al., 2011).

In relation to the analysis of the fungal endophytic community of plants, it is certainly a big challenge that has been progressively overcome by science. The presence of these microorganisms within plant tissues is difficult to be visualized, the hyphae are rarely observed, and distinctive characteristics are scarce (Rashmi et al., 2019). The endophytic community has been traditionally assessed through isolation from surface-sterilized plant tissues, aiming for the recovery of fungal strains present only in the inner of the plant. Therefore, conventional culture media are used, including modifications when necessary, such as the addition of a higher proportion of water in the medium aiming to avoid an osmotic shock and favor the access of exploratory hyphae. Further, the addition of plant extracts in the culture media can be adopted (Murphy et al., 2018). The genetic communication between the endophyte and the host plant for the establishment of the interaction is a complex and poorly understood process that involves the selective expression of fungal genes responsible for the production of enzymes and secondary metabolites that aid in colonization (Bayle et al., 2006; Yan et al., 2019, Das et al., 2012). The approximation of the germinative tube of the endophyte to the root causes the loss of apical dominance of the root and the formation of a hyphal penetration apparatus (aspensorium), which enters the root cortex with hyphae of infection, thereby starting the colonization process (Khan et al., 2015). These events promote a balanced activation of plant defense genes, and when the fungus reaches the inner cortex, the hyphae penetrate the plant cell wall and continue

the colonization of adjacent tissues (endoderm, pericycle, xylem, phloem) of the roots and of the soil (Khan et al., 2015; Yan et al., 2019).

4. How fungal endophyte spread?

While the means of propagation or the transmission routes of many endophytic fungi remain to be determined, yet they are broadly transmitted vertically (systemic) and horizontally (non-systemic). Vertically transmitted endophytes are mutualistic, whereas those transmitted horizontally depict antagonism to the host (Saikkonen et al., 1998; Schardl et al., 1991). Horizontal transmission occurs when vegetative propagules or spores are produced by the endophyte and spread to the plant population through the air or via some vector, while vertical transmission consists of the transference of the fungi to the plant progeny via seeds. The *Epichloe* species are one example where the endophyte can be propagated via both routes as long as the ability to produce ascospores on the host plant is retained. Type of vertical transmission occurs via the seed coat and has been reported for class 2 endophytes (Rodriguez et al., 2009). In the case of horizontal transmission, propagation is usually dependent on the reproductive structures of the endophyte, such as spores, that move by wind or rain dispersal, or are moved by a vector, from plant to plant. This can occur via the soil, through air movement or by vectors, *e.g.*, insects. For the class 2 and 3 endophytes, plant colonization likely occurs via infection structures such as appresoria or directly via the hyphal penetration of plant tissues (Ernst, Mendgen and Wirsal, 2003; Gao and Mendgen, 2006).

B. Biodiversity of fungal endophytes

Endophytes have been isolated from plants growing in temperate to the tropic ecosystems, hot deserts, arctic tundra, mangroves, grasslands, savannahs, and cropland ecosystems (Chhipa and Deshmukh, 2019). The characterization of the endophytic fungi diversity in a host plant by cultivation-dependent methods is considered limited and can be influenced by several biotic and abiotic factors (Ribeiro et al., 2018; Rashmi et al., 2019; Chen et al., 2020). Tropical and temperate rainforests are the most biologically diverse terrestrial ecosystems on earth represented 60% of the world's terrestrial biodiversity. The high probability that rainforests are a source of biologically active compounds (Strobel and Daisy, 2003). Almost all the plant species (~400,000) harbor one or more endophytic organisms (Anitha et al., 2013). The diversity and numbers of fungal endophytes vary considerably, and their detection depends on biotic, abiotic and experimental factors. Endophyte communities from higher latitudes are characterized by relatively few fungal species,

whereas tropical endophyte is dominated by a small number of classes but a very large number of different endophytic species (Lugtenberg et al., 2016). Endophytic fungi are predominantly ascomycetes that appear to be ubiquitous in nature as they have been recovered from plants adapted to a wide range of ecosystems include hot deserts, Arctic tundra, mangroves, temperate and tropical forests, grasslands and savannahs, and croplands (Lugtenberg et al., 2016); extreme arctic, alpine and xeric environments (Ali et al., 2018). Temperate region endophytes showed host specificity, while tropical region endophytes are less host specific (Chhipa and Deshmukh, 2019).

C. Role on endophytic fungi in ecosystem

Fungal endophytes play crucial roles in ecosystems by protecting plants against many biotic and abiotic stresses, increasing their resilience, and helping plants to adapt to new habitats (Strobel and Daisy 2003; Schulz 2006; Rodriguez et al., 2008; Aly, Debbab and Proksch 2011; Friesen 2013). This corresponds to biotic stresses from which endophytes can provide protection include plant pathogens, insects and nematodes and the abiotic stresses which include nutrient limitation, drought, salination and extreme pH values and temperatures. In return, plants provide spatial structure, protection from desiccation, nutrients and, in the case of vertical transmission, dissemination to the next generation of hosts (Schulz 2006; Aly, Debbab and Proksch 2011). Endophytes may also play a role in the ecosystem by affecting plant growth through antagonistic fungal-fungal interactions. A further role of some fungal endophytes in ecosystems may be to initiate the biological degradation of a dead or dying host plant which starts the process of nutrient recycling (Strobel and Daisy, 2003; Zhang, Song and Tan, 2006; Vega et al., 2010; Aly, Debbab and Proksch, 2011; Boberg, Ihrmark and Lindahl, 2011).

Studies involving clavicipitaceous fungi (Class 1) are more widespread, and the main benefit to plants by these fungal groups is the production of secondary metabolites, mainly alkaloids, that accumulate in plant tissues and present bioactivity against many vertebrates, invertebrates and other pathogens (e.g. fungi) and can also confer tolerance to abiotic stresses (KD and Soyong 2008; Rodriguez et al., 2009; Card et al., 2014; Zhang et al., 2015; Lugtenberg et al., 2016; Chitnisset al., 2020 Card et al., 2016; Das et al., 2012). Among nonclavicipitaceous fungi, research on the knowledge of their endophytic relationship with plants and the analysis of benefits that can be explored in the agricultural context are more widespread among representatives of class 2, which includes several species taxonomically belonging to the

subkingdom Dikarya, which includes the phyla Ascomycota and Basidiomycota (Rodriguez et al., 2009).

D. Fungal endophytes in improving plant performance contributing for sustainable agriculture

1. Conferring biotic stresstolerance

While endophyte-free grass is not toxic to animals, it can become susceptible to insect pests. Epichloe[®] endophytes (class 1) are found in some temperate grass species and their primary symbiotically important contribution is to produce bioactive metabolites in the host plant which act as deterrents to pests and herbivores. The common toxic endophyte, *Epichloe festucae* var. *lolii*, originally present in perennial ryegrass and introduced into New Zealand from Europe, produces three known major secondary metabolites: (i) Lolitrem B, a neurotoxin now known to cause ryegrass staggers (Gallagher, White and Mortimer 1981; Gallagher et al., 1982; Fletcher 1993; Fletcher, Sutherland and Fletcher 1999). (ii) Ergovaline, a metabolite that causes vasoconstriction (Oliver, 2005) resulting in heat stress (Fletcher, 1993; Fletcher, Sutherland and Fletcher, 1999) and in tall fescue it causes the condition referred to as fescue toxicosis (Hoveland 1993; Bacon 1995). (iii) Peramine, is an insect feeding deterrent (Rowan, Dymock and Brimble 1990; Rowan 1993). A novel Epichloe[®] strain (AR1) was introduced 15 years ago which produces neither lolitrem B nor ergovaline but the production of peramine provides resistance to a major insect pest—Argentine stem weevil (ASW) (*Listronotus bonariensis*) (Johnson et al., 2013a). Later discoveries of other novel Epichloe[®] endophyte strains identified another alkaloid present in endophytes, the epoxy-janthitrems (Finch, Fletcher and Babu 2012), which are a type of indole diterpene found only in perennial ryegrass infected with strain AR37 (Tapper and Lane 2004). AR37-infected grasses have broad pesticidal effects against five of the six major pasture pests present in New Zealand (Johnson et al., 2013a). Epichloe[®] endophytes have not only received worldwide recognition for their importance in pasture systems in delivering both economic and sustainable agricultural solutions, but they also represent an excellent model system for investigating various aspects of endophyte biology in addition to exploring both the ecological implications and the molecular basis of the symbiosis.

The root-colonizing facultative endophyte *Piriformospora indica* forms beneficial symbioses with crop plants. It has the potential for use in agriculture, horticulture and floriculture (Oelmüller et al., 2009; Franken, 2012; Qiang et al., 2012; Ansari et al., 2013; Oberwinkler et al., 2013; Unnikumar, Sree and

Varma, 2013; Johnson, Alex and Oelmuller, 2014; Gill et al., 2016). *Piriformospora indica* was originally isolated by Verma et al., (1998) from the rhizosphere of several xerophytic plants located in the Indian Thar dessert, India. This filamentous fungus belongs to the order Sebaciniales in Basidiomycota (Weiss et al., 2004) and confers numerous host benefits, such as the promotion of plant growth, particularly in conditions of nutrient stress, and confers tolerance to a wide range of abiotic stresses (drought, temperature extremes, water, salinity, heavy metals), as well as biotic (root and foliar pathogens) stresses. Original inoculation experiments showed the ability of *P. indica* to colonize plant roots (Verma et al., 1998) and to date, it is renowned for its broad host range, forming symbiotic root interactions with both mono- and dicotyledonous plants, including the agriculturally important barley (*Hordeum vulgare*), and the model plants, tobacco (*Nicotiana tabacum*) and *Arabidopsis thaliana* (Johnson, Alex and Oelmuller 2014). Plants colonized with *P. indica* show an enhanced tolerance to various root and foliar pathogens (Alex and Oelmuller, 2014). The potential of *P. indica* as a biocontrol solution to manage various root diseases in different crop species such as maize (Kumar et al., 2009), tomato (Fakhro et al., 2010), wheat (Serfling et al., 2007; Rabiey, Ullah and Shaw, 2015) and barley (Waller et al., 2005) is evident.

Many other fungal endophytes have been shown to protect host plants from pathogenic fungi. The endophyte *Epicoccum nigrum* isolated from sugarcane is especially known for its biocontrol activity against pathogens, such as *Sclerotinia sclerotiorum* in sunflower, *Pythium* in cotton, phytoplasma bacteria in apple and *Monilinia* spp. in peaches and nectarines (Favaro, Sebastianes and Araujo, 2012). Murphy, Doohan and Hodgkinson (2015b) isolated fungal endophytes from wild barley plants (*Hordeum murinum* subsp. *murinum* L.) and demonstrated that some were able to successfully suppress the activity of seed-borne fungal infections on seeds of cultivated barley.

Fungal endophytes isolated from healthy *Theobroma cacao* tissues have been screened *in vitro* for antagonism against major pathogens of cacao including *Moniliophthora roreri* (causing frosty pod rot), *Phytophthora palmivora* (causing black pod rot) and *M. perniciosa* (causes witches broom) (Mejía et al., 2008). Field trials have assessed the effects of these endophytic fungi and have shown that treatment with *Colletotrichum gloeosporioides* significantly decreased pod loss due to black pod rot and that treatment with *Clonostachys rosea* reduced the incidence of sporulating lesions of *M. roreri* on cacao pods (Mejía et al., 2008).

Lastly, fungal entomopathogens are an important class of endophytes to consider for their anti-insect biocontrol properties (Quesada Moraga, Herrero and Zabalgogezcoa, 2014). They have a unique ability to infect and colonize insects affecting insect survival and reproduction and many, if not all, having the ability to colonize plants (Vidal and Jaber, 2015). Interestingly, most of the commercially produced entomopathogenic fungi can be endophytic for part of their life cycle and include the species of *Beauveria*, *Metarrhizium*, *Lecanicillium* and *Isaria* (Vidal and Jaber, 2015). None of these commercial biocontrol products have made use of their endophytic mode of action however, but at least one such product is able to colonize plants endophytically (Vidal and Jaber, 2015). Entomopathogenic fungi are effective against several root-feeding insects belonging to different orders, such as the root mealy bug, *Cataeno coccusensete*, the sugar beet root maggot, *Tetanops myopaeformis*, the diabroticine rootworms, and the white grubs *Melolontha melolontha* and *Popillia japonica* (Li et al., 2000). The coffee berry borer (*Hypothenemus hampei*) is the most devastating pest of coffee throughout the world. These fungal entomopathogenic endophytes also play a role in soil nitrogen cycling. Behie, Zelisko and Bidochka, (2012) tested the ability of *Metarrhizium robertsii* to translocate insect-derived nitrogen to plants.

2. Conferring abiotic stress tolerance

Fitness benefits conferred by mutualistic fungal endophytes contribute to, or are responsible for, plant adaptation to not only biotic stresses but also abiotic stress by increasing tolerance to drought and water stress, as well as tolerance to high temperature and high salinity (Aly, Debbab and Proksch, 2011). Habitat-adapted stress tolerance of plants conferred by habitat-specific symbionts is an intriguing phenomenon hypothesized to be responsible for the establishment of plants in high stress environments (Rodriguez et al., 2008). A large number of class 2 endophytes have been found to be capable of habitat adaption providing tolerance to habitat-specific selective pressures such as soil pH, temperature and salinity (Rodriguez et al., 2009). Rodriguez et al., (2008) demonstrated that grass species adapted to coastal and geothermal habitats harbor symbiotic fungal endophytes that provide salinity and heat tolerance, respectively.

Leymus mollis (dunegrass) plants from several coastal beach habitats in the USA were shown to be symbiotic with the endophyte *Fusarium culmorum* which, when inoculated into salt-sensitive non-coastal plants, conferred salt tolerance to those plants (Rodriguez et al., 2008). Similar studies were carried out to demonstrate that endophytic fungi aid heat tolerance. The tropical panic

grass, *Dichanthelium lanuginosum*, found growing in geothermal soils in Yellowstone National Park forms a mutualistic symbiotic interaction with the class 2 endophyte, *Curvularia protuberata* which confers heat tolerance (Redman et al., 2002). When root zones were heated up to 65 C, symbiotic plants infected with the endophyte tolerated and survived the heat but separately, neither the fungus nor the plant alone were capable of growing at soil temperatures above 38 C (Marquez et al., 2007). This relationship however is more complex as it was discovered that the endophyte harbors a virus in a tripartite mutualistic symbiosis and that the virus is an essential partner for bestowing heat tolerance to host plants, whereas virus-free endophytes were incapable of conferring this trait (Marquez et al., 2007). These habitat-specific symbionts also have a broad host range and have been shown to be able to confer habitat-specific tolerance to other plant species. For example, an endophyte from coastal plants can colonize the model monocot, rice, and confer salt tolerance, whereas endophytes from other habitats (agricultural, coastal and geothermal) can confer disease resistance but not salt or heat tolerance to the model dicot tomato (Rodriguez et al., 2008). Interestingly, all these endophytes conferred drought tolerance to plants regardless of the habitat of origin (Rodriguez et al., 2008).

Decreased water availability and increased soil salinization is a growing challenge to crop growth in many parts of the world (Egamberdieva et al., 2008; Egamberdieva and Lugtenberg, 2014) and this problem is expected to increase due to climate change effects. The ability of fungal endophytes to confer stress tolerance to plants may provide a novel strategy for mitigating the impacts of global climate change on agricultural plant communities (Rodriguez et al., 2008). Redman et al., (2011) showed that some class 2 fungal endophytes can confer salt and drought tolerance to two commercial rice varieties which were not adapted to these stresses. Moreover, these endophytes reduced water consumption by 20%-30% while increasing growth rate, reproductive yield and biomass of greenhouse grown plants. They also conferred cold tolerance to growth chamber and greenhouse grown plants. These findings indicate that the incorporation of fungal symbionts may be a useful strategy in both mitigating impacts of climate change on major crops.

3. Conferring plant growth improvement

Turning to endophytes that have the potential to promote plant growth, *Piriformospora indica* is known for its promotion of vegetative growth, early flowering, seed setting and seed germination which has been repeatedly observed with species from various plant families (Franken, 2012). An

extensive set of phytohormones and phytohormone signaling networks seem to be involved in mediating plant growth promotional activities which lead to increased early root growth promotion and finally to greater biomass. The extent of growth promotion is typically around 50%, but significant variation exists, due in part to variability in the environmental and experimental conditions in which the plants are grown. Considerable research has been carried out on the mechanism of salt stress tolerance conferred to plants colonized with *P. indica* and this trait has been demonstrated for barley as well as wheat, rice and tobacco and involves the induction of a high antioxidant environment for the detoxification of reactive oxygen species and an enhanced photosynthetic efficiency (Johnson, Alex and Oelmuller, 2014). *P.indica's* wide host benefits as well as its amenability for fundamental biological studies are attractive properties for research and its potential to transform the productivity of agricultural crops sustainably is exciting. With respect to barley, *P. indica* interactions have shown enhanced grain yield (Waller et al., 2005; Murphy, Doohan and Hodkinson, 2014) and at low temperatures with higher nutrient input, it also appeared to trigger flowering earlier and still increase grain yield. These results indicate that *P. indica* could be developed as an effective crop treatment in low temperature-stressed barley and may have the potential to increase crop yield under colder growing environments on the provision that adequate nutrients are supplied (Murphy, Doohan and Hodkinson, 2014). However, despite all of these described benefits, Franken (2012) states that it may be difficult to place *P. indica* on the market because (i) the fungus was first isolated in India and is protected by patent in many countries (international publication number-WO 99/29177) making any commercial prospect reliant on the patent owner to manufacturing it or licensing it for manufacture, and (ii) it sometimes has unexplained negative effects on plant growth. Nonetheless, a powder formulation of *P. indica* has been developed under the trade name 'ROOTONIC' and is currently deployed in field trials in India (Varma et al., 2013; Shrivastava and Varma, 2014). There are also other endophytes of barley that have the potential to be advantageous in agricultural settings. Murphy, Doohan and Hodkinson (2015a) isolated endophytic fungi from wild barley (*H. murinum* subsp. *murinum* L.) and in addition to various other biotic benefits, at least one of these isolates was able to increase grain yield in a nutrient-deficient barley cultivar (by up to 29%). The greatest impact of these endophytic isolates had on grain yield and shoot dry weight was achieved under the lowest nutrient input. Such strains may therefore be able to help by reducing fertilizer inputs while maintaining acceptable yields. Continuing with the theme of improving plant performance,

the class 4 or DSE root-colonizing fungi, that are characterized by their darkly melanized septa, are an interesting group of endophytes that are present in a wide range of terrestrial ecosystems, but are especially common in polar and alpine habitats (Rodriguez et al., 2009). In these cold and water-stressed environments, arbuscular mycorrhizal fungi, the typical mutualists of grass roots at lower altitudes and latitudes, are essentially absent (Newsham, 2011) and it has been suggested that DSE species might act as surrogate mycorrhiza in these habitats (Bledsoe, Klein and Bliss, 1990). Inoculation of monocotyledonous and dicotyledonous plant species with these fungi increases root and shoot biomass, and shoot nitrogen and phosphorous contents. Meta-analyses performed by Newsham (2011) on data from 18 research articles, in which plants had been inoculated with DSE species, indicated that they can enhance plant performance under controlled conditions, particularly when most of the nitrogen is available in an organic form such as proteins, peptides and amino acids in the rhizosphere. Plants apparently do not benefit from DSE species when roots can readily access inorganic nitrogen (Newsham, 2011).

E. Significance of secondary metabolites produced by fungal endophytes in agriculture

Discovering plants that harbor these microbes capable of producing novel bioactive metabolites is the first step. Due to the extraordinary biodiversity of fungal endophytes, they provide a largely untapped opportunity to discover novel natural products with unique chemical structures that have been optimized by coevolution with higher plants. The recent development of screening technologies has revealed the great potential of fungal endophytes for producing novel biologically active compounds with promising medicinal or agricultural applications (Zhang, Song and Tan, 2006; Aly, Debbab and Proksch, 2011; Wu et al., 2015a; Das et al., 2012). These molecules can play an important role in communication between organisms, in plant protection and plant adaptation to habitat and environmental changes. For reasons of safety and environmental problems, many synthetic agricultural agents have been, and will be, removed from the market. Secondary metabolites produced by fungal endophytes provide novel opportunities to control pests and pathogens (Strobel and Daisy, 2003). In subsequent sections we restrict the discussion to those fungal secondary metabolites which have promise for, or are already being used in, agriculture and horticulture.

Schulz (2001) described that certain microbial metabolites are characteristic of certain biotopes, on both an environmental and a taxonomic level. This study indicated that organisms living in unique biotopes or habitats

that are subjected to constant metabolic and environmental interactions will yield even more secondary metabolites than organisms that are not (Schulz, 2001). Therefore, the search for novel secondary metabolites should primarily center on organisms that inhabit unique biotopes. Successful collection of plants harboring endophytes which produce novel and unique natural bioactives requires the identification of plants (i) from unique environmental settings, especially those with an unusual biology, and possessing novel strategies for survival; (ii) that have an ethnobotanical history (used by indigenous peoples) and that are related to the specific uses or applications of interest; (iii) that are endemic, that have an unusual longevity or that have occupied a certain ancient land mass; and (iv) that grow in areas of great biodiversity (Strobel and Daisy, 2003). Expeditions to the Amazonian rain forest have led to the discovery of a wide range of secondary metabolites produced by endophytic fungi (Strobel and Strobel, 2007).

1. Anti-microbials

There are many examples of secondary metabolites from endophytic fungi which are being used, or have promise to be used, against pathogens and pests of horticultural and agricultural plants. An overview of 230 metabolites produced by plant-associated microbial strains, including many fungal endophytes, was published by Gunatilaka (2006). Examples of some well-characterized anti-microbial secondary metabolites from endophytic fungi are presented below in alphabetical order. Several of these compounds have been described by Strobel and Daisy (2003).

Some anti-microbial compounds produced by the sugarcane endophyte *Epicoccum nigrum* (Brown, Finlay and Ward, 1987) have been characterized, such as epicorazines A-B (Bauteet al., 1978), epirodines A-B (Ikawaet al., 1978), flavipin (Bamford, Norris and Ward 1961), epicoccines A-D (Zhang et al., 2007), epipiridones and epicocarines (Wangun and Hertweck 2007). Especially the compounds flavipin and epicorazines A-B have been associated with *E. nigrum* biocontrol activity (Brown, Finlay and Ward, 1987; Madrigal, Tadeo and Melgarejo, 1991; Madrigal and Melgarejo, 1995).

Ambuic acid is an antifungal and anti-oomycete agent from the endophytic fungus *Pestalotiopsis microspora*, isolates of which have been found in many of the world's rainforests. It is active against several *Fusarium* species and against *Pythium ultimum* (Li et al., 2001). It also appears to be a quorum-sensing inhibitor (Fuqua, Winans and Greenberg, 1994).

Colletonoic acid (Bills et al., 2002) is a compound from a *Colletotrichum* sp., isolated from *Artemisia annua*. It shows good anti-bacterial, anti-fungal and anti-algal activities (Hussain et al., 2014). Colletotric acid is a metabolite of *Colletotrichum gloeosporioides*, an endophytic fungus from *A. mongolica*. It displays antimicrobial activity against bacteria as well as against the fungus *Helminthosporium sativum* (Zou et al., 2000). Cordycepsidone A was isolated from the endophytic fungus *Cordyceps dipterigena* and has strong antifungal activity against the plant pathogenic fungus *Gibberella fujikuroi* (Varughese et al., 2012). Cryptocandin is a lipopeptide isolated from *Cryptosporiopsis quercina*, a fungus commonly associated with hardwood species in Europe. It is active against a number of plant-pathogenic fungi, including *Sclerotinia sclerotiorum* and *Botrytis cinerea* (Strobel et al., 1999). It is related to known antimycotic compounds: the echinocandins and the pneumocandins (Walsh 1992). Cryptocin is produced by *C. quercina* (Li et al., 2000) and possesses the most potent activity against the fungus *Pyricularia oryzae*. It also shows strong activity against the plant-pathogenic fungi *Fusarium oxysporum*, *Geotrichum candidum*, *Rhizoctonia solarum* and *S. sclerotiorum*, as well as against the plant-pathogenic oomycetes *Pythium multivium*, *Phytophthora cinnamoni* and *Phytophthora citrophthora* (Li et al., 2000).

Jesterone is produced by *Pestalotiopsis jesteri* from Papua New Guinea and was isolated from an area with moist conditions in which plant pathogens, especially oomycetes, normally thrive. As anticipated, the compound has anti-oomycete activity (Li and Strobel, 2001).

The endophytic fungus *Muscodor albus*, isolated from small branches of *Cinnamomum zeylanicum* (cinnamon tree) (Worapong et al., 2001), effectively inhibits and kills certain other fungi and bacteria by producing a mixture of at least 28 volatile compounds (Strobel et al., 2001). *Muscodor crispans* is an endophytic fungus of *Ananas ananassoides* (wild pineapple) growing in the Bolivian Amazon Basin. The fungus produces a mixture of antifungal and antibacterial volatile organic compounds.

Pestacin and isopestacin are anti-oxidants produced by *Pestalotiopsis microspora*, an endophyte from *Terminalia morobensis* (Strobel et al., 2002; Harper et al., 2003). Both also have anti-microbial activity (Strobel and Daisy, 2003). Phomopsichalasin is a secondary metabolite from the fungal endophyte *Phomopsis* sp. and has antibacterial activity against *Bacillus subtilis*, *Salmonella enterica* and *Staphylococcus aureus* (Horn et al., 1995).

Scandenin was isolated from a *Derris scandens* plant from Pakistan and has strong anti-bacterial activity against *B. megaterium* and good anti-fungal and anti-algal properties (Hussain et al., 2015). It is remarkable that none of the anti-microbial secondary metabolites produced by these endophytic fungi has been found to be produced by bacteria which control plant diseases caused by microbes (Haas and Defago, 2005; Lugtenberg and Kamilova, 2009; Pliego, Kamilova and Lugtenberg, 2011).

2. Anti-insect metabolites

The association of synthetic pesticides with ecological damage has led to research to discover powerful, selective and safe alternatives (Strobel and Daisy, 2003). Until now, biopesticides are only a small part of the pesticide market but their impact is increasing. Several endophytes are known to produce secondary metabolites that have anti-insect properties. The nodulisporic compounds were isolated from the endophyte *Nodulisporium* sp. from the plant *Bontia daphnoides*. Since this discovery the focus is on searching for more *Nodulisporium* spp. and for other producers of more-potent nodulisporic acid analogs (Demain et al., 2000).

Muscodor vitigenus is an endophytic fungus of a liana from the rain forest of the Peruvian Amazon. It produces a single volatile, naphthalene, which acts as an insect repellent which is the active ingredient of common mothballs. Nodulisporic acids are indole diterpenes which exhibit potent insecticidal properties against the larvae of the blowfly. They act by activating insect glutamate-gated chloride channels. It also repels the adult stage of the wheat stem sawfly *Cephus cinctus*.

Some new benzofuran compounds (5-hydroxy-2-(1'-hydroxy-5'-methyl-4'-hexenyl) benzofuran and 5-hydroxy-2-(1'-oxo-5'-methyl-4'-hexenyl)benzofuran) were isolated from an unidentified endophytic fungus from wintergreen (*Gaultheria procumbens*). Both show toxicity to spruce budworm, and the latter one is also toxic to its larvae (Findlay et al., 1997).

Peramine is a pyrrolopyrazine feeding deterrent against the insect pest Argentine stem weevil, and is produced by some *Epichloe*-grass associations (Rowan 1993; Johnson et al., 2013a). Indole-diterpenes are another class of alkaloids known to be produced by *Epichloe* endophytes. *Lolitrein B*, which is unique to *Epichloe*, is an infamous example as it is the major tremorgenic mycotoxin responsible for ryegrass staggers (Gallagher et al., 1984), but it also reduces the growth and development of ASW larvae (Prestidge and Gallagher, 1985).

Discoveries were made in the USA where cattle grazing endophytic tall fescue pastures contracted fescue toxicosis caused by some strains of the fungal endophyte *Epichloe coenophialum*. These strains produce the alkaloid ergovaline which is responsible for the vasoconstriction of blood vessels leading to this debilitating animal health and welfare condition (Bacon 1993, 1995). While ergovaline in its own right does have a pesticidal effect (Popay et al., 1990; Rowan, Dymock and Brimble, 1990), the associated effect of fescue toxicosis and heat stress means that ergovaline is not a useful candidate for controlling pests. However, other secondary metabolites which showed no mammalian toxicity were also discovered in this fungal endophyte host plant association. These included peramine and the lolines, which provide broad spectrum pest resistance (Siegel and Bush, 1994; Schardl, Leuchtman and Spiering, 2004; Young, Hume and McCulley, 2013; Johnson et al., 2013a).

3. Plant-beneficial activities

The endophytic fungus *Daldinia concentrica*, isolated from an olive tree in Israel, produces at least 28 volatile organic compounds which are very promising for post-harvest control. These volatiles protect dried fruits of apricot, plum and raisin from rotting. Moreover, they protect peanuts against *Aspergillus niger*, oranges and tomato paste against *Penicillium digitatum* and grapes against *Botrytis cinerea*. Artificial mixtures of selected volatiles have great promise for application in food industry and agriculture (David Ezra and Orna Liarzi, pers. comm.)

Genomic sequencing of endophytic fungi has indicated that, despite the observation that these organisms contain gene clusters encoding certain secondary metabolites, some are not expressed under standard laboratory cultivation conditions. This raises the question as to which physiological and environmental conditions are required for endophytic fungi to express these secondary metabolites (Brakhage, 2013; Netzker et al., 2015). In some cases, the host genome is required for significant expression of the endophyte's secondary metabolite pathways (Schardl and Panaccione, 2005). For example, plant signaling is required to induce expression of the fungal gene clusters for lolitrem B biosynthesis by *E. festucae* var. *loli* so that it is highly expressed in planta but expression is low or undetectable in culture-grown fungal mycelia (Young et al., 2006). The same applies to other secondary metabolites such as lolines and epoxy-janthitrems of *Epichloe* species that produce little or no compound when grown ex planta (Porter, 1994; Tapper and Lane, 2004), despite attempts to circumvent this under in culture conditions as found with loline production (Blankenship et al., 2001). In other cases, endophyte

secondary metabolites may be triggered by the limitation of food sources, competition with other organisms, the presence of plant components (including exudates), the presence of other fungi and bacteria as well as their metabolites and their presence in plants attacked by pathogens and pests. Several examples of conditions under which the expression of secondary metabolites have been induced are published. For example, flavonoids present in root exudates of host plants induce the expression of *Rhizobium* Nod-factors (Van Brussel et al., 1986). Accordingly, the lack of a host stimulus in culture media may explain why the production of biomolecules by a nascent endophyte isolate is often severely attenuated through subculturing (Li et al., 1998). Because microbes in nature live in communities, growth of various fungi in co-culture with other organisms has been tested. Co-culture can indeed result in activation of silent gene clusters or in strongly increased expression (Ola et al., 2013; Wu et al., 2015b). For reviews on the effects of co-culturing, we refer to Bertrand et al., (2014) and Wu et al., (2015a). An interesting observation is that in the case of co-cultivation between *Aspergillus niger* and actinomycetes, an intimate physical interaction is required to activate silent gene clusters in *Aspergillus niger* (Schroeckh et al., 2009).

4. Heavy metal stress tolerance

Heavy metal contamination due to increased industrialization has recently received attention because heavy metals cannot be itself degraded (Kidd et al., 2009). Toxicity by heavy metals can cause the loss of about 25-80% of various cultivated crops. Heavy metals being very toxic to roots of cultivated crop plants can cause poor development of the root system (Singh et al., 2011). Endophytic fungi possess metal sequestration or chelation systems that increases tolerances of their host plants to heavy metals via enhancements of antioxidative system thereby changing heavy metal distribution in plant cells and detoxification of heavy metal, thus assisting their hosts to survive in contaminated soil (Likar, 2011; Wang et al., 20016). For instance, dark septate root endophytes (DSEs), *Phialocephala fortinii* can produce the black biopolymer melanin, which can be synthesized from phenolics and binds heavy metals (Senesi et al., 1987) that keep heavy metal ions away from living, plant cells (Fogarty and Tobin, 1996). Siderophores being metal-chelating compounds (Bultreys, 2007; Miethke and Marahiel 2007) released from roots into the rhizosphere can be helpful in inhibiting absorption of heavy metals into plant cells as siderophores can form complexes with heavy metals which are not easily absorbed by plant roots. Yamaji et al., 2016 recorded that endophytes *P.fortinii* and *Rhizodermea veluwensis* showed an ability to

produce siderophores that probably affects heavy metal exclusion in the rhizosphere.

F. Commercialization of products produced from fungal endophytes

Discoveries in the fields of fundamental microbial and plant ecology have resulted in commercial products that not only generate revenue and employment, but also provide a major contribution to food production and adaptation to environmental changes. Presently, a number of products based on secondary metabolites of endophytic fungi are on the market or close to market. The use of cryptocandin (Walsh, 1992) and its related compounds has been effective against a number of fungi causing diseases of skin and nails (Strobel and Daisy, 2003). MarroneBioinnovations has licensed *Muscodor albus* and EPA approval for the release of this organism for use in agriculture is expected soon. It literally sterilizes the soil in which it has been placed. It is a potential replacement for methyl bromide (Gary Strobel, pers. comm.), which is now restricted from use in many countries. A strain is already on the market for decontamination of human wastes (Strobel et al., 2001; Strobel and Daisy, 2003). Potential applications of the volatiles produced by the new *M. albus* strains were suggested for treatment of seeds, fruits and cut flowers, as well as for soil (Ezra, Hess and Strobel, 2004). As discussed in the section ‘Anti-microbial volatile compounds’, the endophytic fungus *Daldiniacon centrica* produces a mixture of volatile organic compounds which are very promising for post harvest control of dried fruits and other plant products. Effective and safe mixtures can be assembled from the volatiles produced by *M. crispans*, and these mixtures could have commercial potential (Mitchell et al., 2010). In principle, the products can be used for food, flavoring and preservative purposes because each volatile component is on the FDA GRAS list. Presently, a major company is examining the volatile mixture for use as post-harvest treatment of fruits and vegetables. In the meantime, the product is being used to treat cheeses, and as a treatment of industrial surfaces (Gary Strobel, pers. comm.).

Losses due to neuromuscular diseases and heat stress of sheep and cattle grazing on toxic temperate grasses containing asexual *Epichloe* species expressing lolitrem B or ergovaline are substantial (Johnson et al., 2013a). In the USA, the financial losses caused through fescue toxicosis from cattle grazing tall fescue infected with the ergovaline producing commontoxic endophyte were estimated to be US\$ 1 billion per annum to the beef cattle industry (Hoveland, 1993). In New Zealand, the losses due to ryegrass staggers have been estimated to be worth US\$ 65 million (Imlach et al., 2008) and in

Australia, the losses due to toxic *Epichloe* species causing perennial ryegrass toxicosis have been estimated to be US\$ 68 million in 2012 (Webb-Ware, 2013). *Epichloe* endophytes have been successfully commercialized in perennial ryegrass and tall fescue with different traits and pastoral benefits for New Zealand, Australia, South America and the USA (Young, Hume and McCulley, 2013; Johnson et al., 2013a). The identification of novel *Epichloe* endophytes has resulted in grasses being developed and bred with animal-safe properties (Easton et al., 2001). They can enhance the plants' survival through protection from abiotic and biotic stresses and can therefore be utilized in agriculture. Presently, novel endophyte strains have been rapidly adopted by farmers (Caradus, Lovatt and Belgrave, 2013) and are estimated to contribute approximately US\$ 130 million per annum to the New Zealand economy (Johnson et al., 2013a).

Based on the observation that selected class 2 endophytes are able to confer disease, salt and heat tolerance to grasses (Rodriguez et al., 2008) and the subsequent finding that these tolerances can be transferred to agricultural plants (Rodriguez et al., 2008; Redman et al., 2011), these endophytes have been commercialized to improve agriculture in relation to climate changes, which may give rise to water, drought and salination stresses. The products include BioEnsureR -Corn and BioEnsureR -Rice. BioEnsureR -Corn is promoted to have a 25%-80% yield increase under heavy drought stress and even a 7% yield increase under low drought stress. These plants also use 25%-50% less water under normal conditions as well as under low drought stress. BioEnsureR -Rice is promoted to cause a yield increase under drought and salt stresses as well as a 25%-40% decreased water use. The products are sold as liquid formulations that are sprayed onto seeds by commercial seed treatment companies. The fungi remain dormant on the seed until germination when they establish a symbiotic association with seedlings.

G. Recommendations for agriculture domain

Since fungal endophytes may hold the key to future opportunities for a sustainable agricultural, we must focus on capturing the benefits of these beneficial microbes with some urgency. In germplasm centers, recognition is to be given to likelihood that seed may contain numerous fungal endophytes that may have scientific and economic importance. Storing seed at low temperature and low humidity will not only benefit the longevity of the seed itself but also the viability of any fungal endophytes they may contain. In addition, ensure that high temperature and fungicidal treatment of seed are avoided. For plant breeders, acclimation will be that the crop of importance is often benefited by

fungal endophytes and suggest that they (i) check whether known beneficial microbes are lost during their breeding procedures, (ii) adapt their protocols in order to include the microbiomes, (iii) collect and sequence DNA from seeds of plants from the centers of origin before they are being propagated to identify the presence of potentially beneficial endophytes and (iv) check whether propagation and treatment of seeds from centers of origin results in the loss of beneficial microbes, and loss or mutation of genes. To seed companies, the recommendation will be to (i) check whether heat treatment and the use of synthetic as well as biological fungicides in seed coatings kills or weakens beneficial microbes within or on the seeds, (ii) check whether substances present in seed coatings kill beneficial microbes during storage and during germination (iii) and if possible, store seed containing beneficial and economically important fungal endophytes at low temperature and low humidity. To plant microbiologists, we suggest that they (i) preserve and sequence all microbiomes of plants from the centers of origin, (ii) identify from these collections microbes beneficial in an agricultural and horticultural context and (iii) search for novel microbial beneficial secondary metabolites, especially from the centers of origin and from tropical rain forests. To politicians, opinion makers and the public, it is to be requested that they have an increased awareness of the importance of (i) plant microbiomes for plant health and food production, and (ii) the preservation of wild plants and their microbiomes in their habitats. Annually, the loss of natural habitats through clearing, harvesting, fire, agricultural development, mining or other human-oriented activities results in the inevitable loss of not only plant species of importance but also of fungal endophytes.

Conclusion

Being safe, cost-effective, have ability to produce various compounds like phytohormones, defensive compounds, solubilize phosphates, extracellular enzymes, siderophore production, inhibiting plant pathogens, and promoting plant growth, the fungal endophytes can be a significant component of sustainable agriculture. Over the last decade, sharp rise in study of fungal endophytes is seen as they hold huge potential to contribute to agricultural sector. However, most of the research on endophytes is still at an experimental level in lab or greenhouse. For permitting the practical use of these endophytes in agriculture it is extremely necessary to encourage field experiments to determine the effectiveness of the endophytes under real world conditions. Simultaneously, it is also necessary to build awareness of this new research field among farmers to improve interactions and collaboration with scientists

working in different fields, thereby encouraging the adoption of endophytes in agriculture and maximizing their benefits. If fungal endophytes become feasible in agricultural sector, their practical aspects will also have to be researched so that the farmers can learn how to integrate these novel endophyte species within pre-existing eco-friendly agricultural methods so as to ensure continuity in the approach to sustainability. Moreover, scientific research has to be also focused on use of genetically modified endophytes made by combining endophytes having two or more different ecological roles, such as the suppression of diseases and insect pests to simultaneously improve plant yields and its defensive properties. Thus, optimization of microbial functions of fungal endophytes to enhance crop production and protection is also required for a optimized sustainable agriculture.

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Access this Chapter in Online	
	Subject: Endophytes
Quick Response Code	
DOI: 10.22192/enmpgp.2021	

How to cite this Chapter:

Kuntal Das; R.K.S. Tiwari; Sumana Das. (2021). Role and significance of endophytic fungi in crop improvement for sustainable agriculture: Current perspective and future trend . Sonali Priyadarshini, S. Panigrahi and C. C. Rath. (Eds), Endophytes: Novel Microorganisms for Plant Growth Promotion. India: Darshan Publishers. pp: 29-91.

Fungal endosymbionts in algae: Ecology and application

**Smrutirekha Mishra, Barsha B. Swain and
Pradipta K. Mohapatra***

Department of Botany, Ravenshaw University, Cuttack-753 003, India

*Corresponding author: pradiptamoha@yahoo.com

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1. Introduction

The endophytes are the endosymbiotic organisms, especially the microorganisms that colonize the cells of photoautotrophic hosts. There is an extensive range of potential hosts and endosymbionts that not only stay together but also grow in association with each other extending mutual benefits. The cluster often includes bacteria (Kobayashi & Palumbo 2000), fungi (Stone et al. 2000), algae (Peters 1991), and insects (Feller 1995). In contrast to the broad-range usage of the term ‘endophyte’, many mycologists use this term only for those fungi that live within a plant tissue without causing any significant disease symptom at any determined moment (Stone et al. 2000).

Bacteria and fungi can be found everywhere in nature and exhibit complex interactions with their hosts, in which they maintain a wide range of relations such as mutualism, antagonism and also parasitism (Nair & Padmavathy 2014).

Macroalgae, especially the marine ones, are colonized by a diverse group of microorganisms that interact with them throughout their life cycle. Within this large microbial diversity, bacteria have been extensively studied, yet macroalgae also harbor a large diversity of fungi. Fungal communities associated with these algae have profound effects on their growth, defense, development and nutrition (Egan et al. 2013). The first report of an obligate mycophycobiosis between the Fucales *Ascophyllum nodosum*, *Pelvetia canaliculata*, and the fungal endosymbiont *Stigmatidium ascophylli* dates back to more than a century (Cotton 1907; Stanley 1991). Since then many a different fungal endosymbionts and algal hosts have been identified and their interactions have been extensively studied. There are numerous reports on ecological, industrial, pharmaceutical and agricultural importance of the fungal endophytes of algal origin. This chapter aims to provide an overview of endophytic fungi in algae, summarize the findings of the endophytic fungal diversity, their ecological distribution and application potential.

2. Fungi-algae endophytic association

Bacteria, actinomycetes, mycoplasma and fungi may exist as endophytes among various microorganisms (Rajamanikyam et al. 2017) and the relationship between endophytes and their host plant is highly complex (Nair and Padmavathy 2014). The endosymbionts get space and nutrition to grow and, in return, support the green host in numerable ways. Many fungi, mostly the filamentous ones, asymptotically colonize the algal inner tissues without causing any apparent damage or disease (Debbab et al. 2012). In algal species, the endophytes improve the physiology and stabilize their growth pattern by secreting a number of growth factors. They also increase the absorption of mineral nutrients by the algal hosts and thus maintain the nutritional balance of carbon, nitrogen, oxygen, phosphorus and many others, even under the conditions of nutrient deficiency. If the endosymbiont colonize a host plant and the host tissue appears to be stable, the association can be of various types such as latent pathogenesis, parasitism, commensalism or even mutualism but never reach to the intimacy of symbiosis, thus demonstrating that there is unequal sharing of benefits between the host and the symbiont in the endophytic association (Hardoim et al. 2015; Rédou et al. 2016). While parasitism is the most exploitative by the endosymbiont at the cost of the host,

mutualistic interactions benefit both the host and endophytes in the presence of each other.

The algal endophytes have been mostly studied in case of marine micro- and macroalgal flora. The macroalgae that exist in the marine ecosystem are constantly exposed to different levels of biotic and abiotic stresses such as prolonged periods of sunlight exposure, moisture and salt concentration variation, changing tides, abundant microorganisms and herbivore insects (Sarasan et al. 2017). However, they are able to adapt to such environmental variations by the cooperative functions of the endophytes. Some researches indicated that fungus inhabiting the intercellular and intracellular spaces of various marine algae not only improve the host's ability to withstand a variety of such abiotic and biotic stresses, but also enhance their resistance to various environmental stresses and other parasitic organisms. The stress that the marine algae face, causes the endophytes to produce bioactive secondary metabolites, which reinforces the host's defense system (Bramhachari et al. 2019). The endophytes receive shelter and nutrients for growth in return (Tadych & White 2019). The quantitative and qualitative variation of the secondary metabolites are used as the measure of the magnitude of presence of the fungal endophytes in the algal cells. While observing the marine algal hosts and isolating the fungal strains present in them, it can be concluded that the amount of bioactive compounds accumulated is proportional to the amount of fungal population that inhabit the algal thallus.

2.1 Fungal endophytes of algal hosts

Morphological identification of endophytes has proved to be low in sensitivity and specificity, because of several limitations. Different culture media and environmental conditions have a great influence on the phenotype and therefore cannot be definitive for accurate identification. In addition, many endophytes do not sporulate under laboratory conditions and only hyphae and some non-specific structures are present, making it difficult for accurate species level identification (Jeewon et al. 2013; Chin et al. 2021). Nonetheless, extensive studies made on ecology and physiology of different endophyte bearing hosts have shown that the fungal members of genera *Acremonium*, *Arthrinium*, *Alternaria*, *Aspergillus*, *Cladosporium*, *Fusarium*, *Penicillium*, *Phoma* and *Trichoderma* are significantly associated with marine algae as well as terrestrial plants, wood and soils (Stanley 1992; Kohlmeyer & Volkmann-Kohlmeyer 2003; Zuccaro et al. 2008; Jeewon et al. 2013; Du et al. 2017; Vallet et al. 2018; Chin et al. 2021)(Table 1). However, other fungal species of genera *Spathulospora*, *Chadefaudia*, *Haloguignardia*, *Retrostium*,

Histopidicarpomyces and *Pontogenia* all are found particularly in marine algae (Zuccaro & Mitchell 2005; Suryanarayanan et al. 2010; Yang et al. 2018).

Algal samples that were collected from various habitats have shown that most of the endophytic fungi belong to Ascomycota. However, Raveendran & Manimohan (2007) reported that the algae of the Munambam and Varkala coastline have endophytes belonging to basidiomycetes, while some obtained from algae sampled along Varkala coastline belonged to ascomycetes. Basidiomycetian fungi are very rarely reported in marine habitats because it is unsuitable for them to adapt to marine conditions due to their large putrescent fruit bodies and spore-discharge mechanism. There are only few basidiomycetes documented from marine habitats whereas ascomycetes are the most dominant group in marine mycology, which is because of their inbuilt ability to withstand fluctuating saline conditions along with small sporocarps. Various strains of the fungal genus *Eurotium*, including *E. cristatum*, *E. rubrum*, *Eurotium* sp. and *E. herbariorum*, have been characterized from the brown alga *Sargassum thunbergii*, red alga *Asparagopsis taxiformis* and *Bostrychia tenella* and green alga *Epiactis prolifera* (Li et al. 2013; Du et al. 2017).

2.1 Algal hosts

Algae derived from the marine territory are the excellent sources of endophytic fungus (Debbab et al. 2011). From the ecological studies of marine algae and their associated endophytes, it has been found that most of the algicolous fungi are generally associated with the members of algal genera *Ascophyllum*, *Ceramium*, *Ceratodictyon*, *Chondrus*, *Cladophora*, *Dilsea*, *Egregia*, *Enteromorpha*, *Fucus*, *Halymenia*, *Hypnea*, *Laminaria*, *Porphyra*, *Saccorhiza*, *Sargassum*, and *Ulva* (Kohlmeyer & Volkmann-Kohlmeyer 1991; Stanley 1992; Zuccaro & Mitchell 2005; Zuccaro et al. 2008; Suryanarayanan et al. 2010; Suryanarayanan 2012; Jeewon et al. 2019; Chin et al. 2021)(Table1). Different literature survey shows that brown algae has the maximum fungal endophyte colony followed by red and green algae (Fig. 1). Since the Chlorophyceae members have comparatively short life cycle and also the endosymbionts have slow growth, this together might have been the reason for the low fungal diversity and bioactivity in green algae (Zuccaro & Mitchell 2005). However, the dominance of the algal group with fungal endophytes have some habitat specificity. From another experimental research conducted by collecting macroalgae from various marine and freshwater sources of Israel, to test the ability of endophytes to inhibit the aquaculture pathogens, it was found that algae from the phylum Rhodophyta had the highest percentage of

active isolates (49.5%), while the phylum Chlorophyta had the least. The alga *Padina pavonica* of the phylum Ochrophyta had the maximum endophytic association. The only cyanobacteria sampled was *Leptolyngbya* sp., and it had the lowest percentage of bioactive isolates (Deutsch et al. 2021). The percentage of active isolates gives us the idea about their colonization within the host algal family.

In a research conducted by Flewelling et al. (2013) for Isolation and bioassay screening of fungal endophytes from North Atlantic marine macroalgae, it has been reported that out of 3000 algal samples studied, only 594 fungal endophytes were isolated. The isolation frequencies of endophytic fungi differed by the hosts. The highest isolation frequencies were seen in red alga *Polysiphonia lanosa* and the brown alga *Fucus serratus* at rates of 38% and 33%, respectively. The lowest isolation frequencies were from the red alga *Porphyra* sp. and the green alga *Ulva lactuca* at rates of 1% and 7%, respectively. From the distinct endophytic species that have been extracted from the algal hosts, *Penicillium* sp. and *Aspergillus* sp. were found to be of the highest occurrence (Flewelling et al. 2013). Since *Aspergillus* and *Penicillium* were found to be surviving on a wide range of algal hosts, it can be deduced that these species are flexible in terms of host specificity and can be considered as facultative marine fungi.

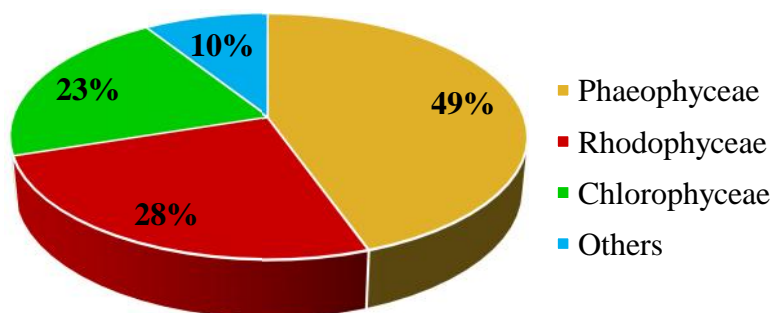


Figure 1. Proportionate representation of reported macroalgal hosts with endophytic fungi.

Further, when rarefaction curves were plotted for each algal class to determine the endophytic diversity in North Atlantic Region, it was seen that green algae possessed the highest diversity of endophytes, whereas the brown

algae had the lowest species diversity (Flewelling et al. 2013). However, when similar rarefaction curves were plotted by Suryanarayanan et al. (2010), on the basis of isolation of endophytes from marine algae collected from Tamil Nadu, the results were notably different from the Shetland Island isolates. Their reports explained that green algae from Tamil Nadu yielded the lowest diversity of endophytic fungal species and brown algae the highest (Flewelling et al. 2013).

Table 1. The endosymbionts and their algal hosts of algae-fungi endophytic association. The list have been compiled from Raghukumar et al. (1992), Zuccaro et al. (2008), Schulz et al. (2008), Suryanarayanan et al. (2010), Suryanarayanan (2012), Harvey and Goff (2010), Du et al. (2017), Yang et al. (2018), Vallet et al. (2018), Harikrishnan et al. (2021) and Chin et al. (2021).

Sl. No.	Fungal endophyte	Algal host
1	<i>Acremoniella</i> sp.	<i>Padina tetrastromatica</i>
2	<i>Acremonium</i> sp., <i>Acroconidiella</i> sp., <i>Asteromyces cruciatus</i> , <i>Botrytis cinerea</i> , <i>Dendryphiella salina</i> , <i>Emericellopsis minima</i> , <i>Epicoccum</i> sp., <i>Geomyces</i> sp., <i>Gliocladium</i> sp., <i>Humicola fuscoatra</i> , <i>Lindra obtusa</i> , <i>Microascus</i> sp., <i>Mycosphaerella</i> sp., <i>Nodulisporium</i> sp., <i>Periconia</i> sp., <i>Scopulariopsis</i> sp., <i>Sigmodocea marina</i> , <i>Verticillium cinnabarinum</i>	<i>Fucus serratus</i>
3	<i>Acremonium</i> sp.	<i>Turbinaria conoides</i>
4	<i>Acremonium sclerotigenum</i> , <i>Pseudopithomyces madicus</i>	<i>Sargassum porterianum</i>
5	<i>Alternaria</i> sp.	<i>Fucus serratus</i> , <i>Gelidiella acerosa</i> , <i>Stoechospermum marginatum</i> , <i>Sargassum</i> sp., <i>Turbinaria conoides</i> , <i>Ulva linza</i>
6	<i>Aphanocladium</i> sp.	<i>Gracilaria</i> sp.
7	<i>Arthrinium</i> sp.	<i>Fucus</i> sp., <i>F. serratus</i>

8	<i>Aspergillus</i> sp.	<i>Ascophyllum nodosum</i> , <i>Caulerpa racemosa</i> , <i>C. scalpelliformis</i> , <i>C. sertularioides</i> , <i>Chondrus crispus</i> , <i>Dictyota dichotoma</i> , <i>F. serratus</i> , <i>G. acerosa</i> , <i>Gracilaria crassa</i> , <i>G. edulis</i> , <i>Grateloupia lithophila</i> , <i>Halimeda macroloba</i> , <i>Halymenia</i> sp., <i>Lobophora variegata</i> , <i>Padina tetrastromatica</i> , <i>P. gymnospora</i> , <i>Portieria hornemannii</i> , <i>S. marginatum</i> , <i>Sargassum</i> sp., <i>S. ilicifolium</i> , <i>S. wightii</i> , <i>Turbinaria</i> sp., <i>T. conoides</i> , <i>T. decurrens</i> , <i>Ulva intestinalis</i> , <i>U. fasciata</i> , <i>U. lactuca</i>
9	<i>Aspergillus</i> sp., <i>Penicillium chrysogenum</i> , <i>P. soppii</i>	<i>Saccharina latissima</i>
10	<i>Aspergillus sydowii</i>	<i>Laurencia okamurai</i> , <i>Porphyra umbilicalis</i>
11	<i>Aspergillus unguis</i> , <i>Hypoxylon fragiforme</i> , <i>Perenniporia</i> sp., <i>Rigidoporus vinctus</i>	<i>Enteromorpha</i> sp.
12	<i>Aspergillus</i> sp., <i>Penicillium crustosum</i>	<i>Chondrus crispus</i>
13	<i>Aspergillus nidulans</i> , <i>A. niger</i> , <i>Colletotrichum gloeosporioides</i> , <i>Daldinia eschscholtzii</i> , <i>Penicillium cinnamopurpureum</i> , <i>Pestalotiopsis</i> sp., <i>Pichia kudriavzevii</i>	<i>Chaetomorpha</i> sp.
14	<i>Aspergillus penicillioides</i> , <i>Curvelaria lunata</i>	<i>Turbinaria conoides</i>
15	<i>Aureobasidium pullulans</i>	<i>Caulerpa racemosa</i> , <i>Devaleraea ramentacea</i>
16	<i>A. pullulans</i> , <i>Botryotinia fuckeliana</i>	<i>Polysiphonia lanosa</i>
17	<i>Botrytis</i> sp., <i>Cladosporium</i> sp.,	<i>Devaleraea ramentacea</i>

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	<i>Coniothyrium</i> sp., <i>Penicillium decumbens</i> , <i>Trametes versicolor</i>	
18	<i>Botrytis</i> sp., <i>Helicomyces</i> sp., <i>Hypoxylon</i> sp., <i>P. chrysogenum</i> , <i>P. decumbens</i> , <i>P. crustosum</i>	<i>Palmaria palmata</i>
19	<i>Candida railensis</i>	<i>Ulva</i> sp.
20	<i>Chaetomium globosum</i>	<i>Polysiphonia urceolata</i>
21	<i>Chaetomium</i> sp.	<i>C. racemosa</i> , <i>C. sertularioides</i> , <i>Ceramium</i> sp., <i>F. serratus</i> , <i>H. macroloba</i> , <i>L. variegata</i> , <i>Padina tetrastrumatica</i> , <i>P. gymnospora</i> , <i>S. marginatum</i> , <i>Turbinaria</i> sp., <i>T. conoides</i> , <i>T. decurrens</i> , <i>Ulva fasciata</i> , <i>U. lactuca</i>
22	<i>Cladosporium</i> sp.	<i>C. racemosa</i> , <i>C. sertularioides</i> , <i>Dictyota</i> sp., <i>F. serratus</i> , <i>Grateloupia lithophila</i> , <i>Halymenia</i> sp., <i>P. gymnospora</i> , <i>Portieria hornemannii</i> , <i>S. wightii</i> , <i>Turbinaria</i> sp., <i>T. conoides</i> , <i>U. lactuca</i>
23	<i>Colletotrichum</i> sp.	<i>Sargassum</i> sp., <i>Turbinaria</i> sp.
24	<i>Coniothyrium</i> sp.	<i>Corallina elongata</i> , <i>F. serratus</i>
25	<i>Corollospora</i> sp.	<i>F. serratus</i> , <i>Sargassum</i> sp.
26	<i>Curvularia</i> sp.	<i>C. scalpelliformis</i> , <i>Turbinaria</i> sp., <i>T. decurrens</i> , <i>Ulva fasciata</i>
27	<i>Cystoblastidium minutum</i>	<i>Rhizoclonium</i> sp.
28	<i>Drechslera</i> sp.	<i>Halymenia</i> sp., <i>Sargassum</i> sp., <i>Turbinaria</i> sp., <i>T. decurrens</i>
29	<i>Emericella nidulans</i>	<i>Halymenia</i> sp., <i>Lobophora variegata</i> , <i>S. marginatum</i> , <i>S. wightii</i> , <i>Turbinaria</i> sp., <i>T. conoides</i> , <i>T. decurrens</i>

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30	<i>Eurotium cristatum</i>	<i>Sargassum thunbergii</i>
31	<i>Eurotium rubrum</i>	<i>Asparagopsis taxiformis</i>
32	<i>Eurotium</i> sp.	<i>Bostrychia tenella</i>
33	<i>Eurotium herbariorum</i>	<i>Epiactis prolifera</i>
34	<i>Fusarium</i> sp.	<i>Caulerpa racemosa</i> , <i>C. sertularioides</i> , <i>F. serratus</i> , <i>Turbinaria</i> sp.
35	<i>Geniculosporium</i> sp.	<i>Polysiphonia</i> sp.
36	<i>Grammothele fuligo</i>	<i>Undaria</i> sp.
37	<i>Haloguignardia</i> sp.	<i>Cystoseira</i> sp., <i>Halidrys</i> sp.
38	<i>Helicosporium</i> sp.	<i>Sargassum</i> sp.
39	<i>Lindra thalassiae</i>	<i>Sargassum cinereum</i>
40	<i>Memnoniella</i> sp.	<i>Portieria hornemannii</i>
41	<i>Monilia</i> sp.	<i>Gracilaria</i> sp.
42	<i>Monodictys</i> sp.	<i>Padina tetrastrumatica</i> , <i>Turbinaria</i> sp.
43	<i>Mucor</i> sp.	<i>C. racemosa</i> , <i>F. serratus</i>
44	<i>Myrothecium</i> sp.	<i>Caulerpa sertularioides</i>
45	<i>Nigrospora</i> sp.	<i>L. variegata</i> , <i>S. marginatum</i> , <i>Sargassum</i> sp., <i>S. wightii</i> , <i>T. decurrens</i> , <i>U. lactuca</i>
46	<i>Oidiodendron</i> sp.	<i>F. serratus</i> , <i>S. wightii</i>
47	<i>Paecilomyces</i> sp.	<i>C. scalpelliformis</i> , <i>F. serratus</i> , <i>Gracilaria</i> sp., <i>G. edulis</i> , <i>Halymenia</i> sp., <i>H. macroloba</i> , <i>P. tetrastrumatica</i> , <i>S. wightii</i> , <i>Turbinaria</i> sp., <i>U. fasciata</i>
48	<i>Penicillium</i> sp.	<i>C. racemosa</i> , <i>C. scalpelliformis</i> , <i>C. sertularioides</i> , <i>F. serratus</i> , <i>F. vesiculosus</i> , <i>G. acerosa</i> , <i>Halymenia</i> sp., <i>H. macroloba</i> ,

		<i>Padina tetrastrumatica</i> , <i>P. gymnospora</i> , <i>Portieria hornemannii</i> , <i>Sargassum</i> sp., <i>S. wightii</i> , <i>U. lactuca</i>
49	<i>Penicillium chrysogenum</i>	<i>Ulva lactuca</i>
50	<i>Penicillium</i> sp., <i>P. decumbens</i>	<i>Mastocarpus stellatus</i>
51	<i>Penicillium spinulosum</i> , <i>P. soppii</i>	<i>Spongomorpha arcta</i>
52	<i>Penicillium citrinum</i>	<i>Laurencia okamurai</i>
53	<i>Phaeotrichoconis</i> sp.	<i>Turbinaria</i> sp.
54	<i>Phialophora</i> sp.	<i>C. sertularioides</i> , <i>Turbinaria conoides</i> , <i>T. decurrens</i>
55	<i>Phoma</i> sp.	<i>C. racemosa</i> , <i>F. serratus</i> , <i>F. vesiculosus</i> , <i>G. acerosa</i> , <i>Halymenia</i> sp. <i>P. gymnospora</i> , <i>T. conoides</i>
56	<i>Phomopsis</i> sp.	<i>F. serratus</i> , <i>P. hornemannii</i>
57	<i>Pleosporales</i> sp.	<i>Ulva</i> sp.
58	<i>Pyrenochaeta</i> sp.	<i>Caulerpa racemosa</i>
59	<i>Taeniolella</i> sp.	<i>Sargassum</i> sp.
60	<i>Tolypocladium inflatum</i>	<i>Fucus vesiculosus</i>
61	<i>Trichoderma</i> sp.	<i>D. dichotoma</i> , <i>F. serratus</i> , <i>G. crassa</i> , <i>H. macroloba</i> , <i>P. gymnospora</i>
62	<i>Trimmatostroma</i> sp.	<i>Portieria hornemannii</i>
63	<i>Varicosporium</i> sp.	<i>Sargassum</i> sp., <i>Turbinaria</i> sp.

3. Ecology of algae-fungal endophyte association

The ecological condition of the habitat is a strong determinant of the initiation, establishment and continuation of the endophytic association between algae and fungi. Algae growing in the habitat with optimum salinity, temperature and pH show minimum endophyte infection since the comfortable

growth conditions do not activate the association. On the other hand, the nutrient and salinity stressed conditions force the algae to facilitate the fungal hyphae deep into the tissue and provide all conditions for the active growth of the endophyte. Chai et al. (2016) opined that the functions of endophytes depend on the nature of the microhabitat of endophytic fungi within the host. The latter, in the process of self protection, also increases the resilience of the host from a wide range of extreme environmental conditions such as desiccation and drought. In case of marine microalgae, the association provides protection from desiccation as long as 8 hr whereas unassociated algae are stressed within 2 hr (Wicklow et al. 2005). Waqas et al. (2015) noticed that the ability of fungus to survive in a high-stress environment is one of the factors that allows endophytic fungi to have a high magnitude of resistance and tolerance to extreme environmental variations.

The algae-endophyte interaction depends on the endophytic niche. Competition of ecological niche and nutrition, hyperparasites and predation are between diverse microorganism that live in endophytic niche, especially between endophytes and pathogens. Endophytic recognition and colonization rapidly occupy ecological niche and leave no space for pathogens, which would be the common and main reason that fungal endophytes inhibit pathogen infection in the host. Fungal endophytes have the ability to colonize inter- or intracellular regions and often are localized in single cell. The colonization of algal cells by endophytes involves several steps including host recognition, spore germination, penetration of the epidermis and tissue colonization (Petrini 1991; 1996). After endophytes are successfully colonized in host tissue, the endophytic niche becomes established. In the endophytic niche, endophytes will obtain a reliable source of nutrition provided from host tissues, exudates and leachates and protect the host against other microorganisms. Fungal endophytes are generally thought to protect the host by rapid colonization and thereby exhausting the limited available substrates so that none would be available for pathogens to grow (Pal & Gardener 2006). Hyperparasitism is another ecological strategy that endophytes provide to protect host plants. In this case, the pathogen is directly attacked by a specific endophyte that kills it or its propagules thereby effectively controlling the occurrence of pathogenesis (Tripathi et al. 2008). Fungal endophytes parasitize around hyphae by various means such as twisting, penetrating the hyphae of pathogens and secreting lyase to decompose the cell wall of pathogens. Some endophytes also show predatory behavior under nutrient-limited conditions.

4. Applications of algicolous endophytes

With a widespread diversity as well as atypical lifestyle, endophytes have exceptional synthetic ability to produce a high diversity of chemicals to counteract a wide range of host defense molecules for colonizing the hosts and draw nutrition from them (Gouda et al. 2016; Khare et al. 2018). Therefore, these heterotrophic fungal partners qualify the criteria for having the ability to produce novel compounds, which can meet the pharmaceutical needs of today's era (Selim et al. 2012). However, the macroalgal colonised endophytic fungi have the ability to mimic and improve the quality of copied metabolite compounds produced by its host (Radi & Štrukelj 2012). As a counter benefit the algae are advantaged, like in case of higher plants, by the fungal endophyte through increased production of growth promoters, boosted up defense mechanism, uplifted nutritional uptake, protection against biotic and abiotic stress, etc. (Santoyo et al. 2016; Khare et al. 2018). Some reports emphasize the importance of endophytes in removal of xenobiotics in the bioremediation process (Ma et al. 2011). Due to the diversity of their secondary metabolites, endophytes act as potential sources of novel compounds of diversified chemical nature, viz. alkaloids, steroids, flavonoids, and terpenoids (Guo et al. 2008). Endophytic fungi have the ability to target various fields such as pharmaceuticals, industries, ecological bioremediation, etc.

4.1. Pharmaceutical importance

The marine algal sourced endophytic fungi are good source of metabolites with various biological activities against human pathogens (Table 2). The paclitaxel (taxol) is the most commonly used chemical agent that checks the cancerous cell growth and prevention of different types of cancer. The compound taxol is produced from marine endophytic fungus *Metarhizium anisopliae* and *Cladosporium cladosporioides* (Gond et al. 2014). Cladosporin, epiepotormin and phyllistine are antibacterial compounds that are produced by *Penicillium* sp., endophytic on Brown alga *Fucus spiralis*. *P. spartinae*, endophyte in marine alga *Ceramium* sp., produces spartinoxide and spartinol C, that are potent inhibitors of the enzyme human leukocyte elastase. Dreschslerins are antimalarial compounds against *P. falciparum* extracted from fungus *Drechslera dematioidea* endophytic on red alga *Liagora viscida*. *Penicillium* sp. of red alga *Polysiphonia urceolata* endophyte synthesises cephalosorolides H and I, which are xanthine oxidase and steroid dehydrogenase inhibitors. *Chaetomium* sp. from *Caulerpa racemosa* synthesises an enzyme inhibitor named Chaetominedione, which is used for the treatment of nutritional deficiencies. Endophytic fungus *Aspergillus versicolor*

in green alga *Halimeda opuntia* potentially inhibits the hepatitis C virus by producing various chemical compounds such as siderin, arugosin C and vericulano. Aquastatin A is a novel therapy for type II diabetes and obesity and has been produced by the inter-tidal endophytic fungi *Cosmospora* sp., which competitively and selectively inhibited protein tyrosine phosphatases. The latter are a group of enzymes responsible for modulating tyrosine phosphorylation-dependent cellular events (Bugni & Ireland 2004). Cultures of *Chaetomium globosum*, isolated from the marine green alga *Ulva pertusa* (Ulvaceae) collected from China coast line, yields seven new cytochalasan derivatives, cytoglobosins A–G with activity against P388, A549, and KB cancer cell lines, and cytotoxic activity toward the A549 cancer cell (Jeewon et al. 2019). Chemical investigation of *Aspergillus ochraceus*, isolated from the marine brown alga *Sargassum kjellmanianum* showed the presence of 7-nor-ergosterolide (Chanda et al. 2010).

The metabolites of *Gibberella zeae* isolated from the marine alga *Codium fragile* showed anticancer activity (Liu et al. 2011). Metabolites derived from *Penicillium chrysogenum* from the marine alga *Sargassum pallidum* also showed anticancer activity (An et al. 2013). The metabolites Aspewentin A–C derived from *Aspergillus wentii*, endophytic on *Sargassum fusiforme*, have anticancer activity (Miao et al. 2012). *Aspergillus niger* isolated from *Colpomenia sinuosa* was reported to produce isopyrophene, aspergillusol, and pyrophene with anticancer activity (Flewelling et al. 2015). Kumari et al. (2018) demonstrated the antiproliferative effect of the ethyl acetate extract of *Talaromyces purpurogenus* isolated from brown algae and Vasavi et al. (2019) reported the anticancer and free radical scavenging effect of ethyl acetate extract of the endophytic fungus *Cladosporium uredinicola* from *Dictyota dichotoma*. A new polyoxygenated decalin derivative, dehydroxychlorofusareilin B, obtained from extracts of *Aspergillus* sp. from *Sargassum horneri*, showed mild antibacterial activity against *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), and multidrug-resistant *S. aureus* (Debbab et al. 2010; Jeewon et al. 2019). Liu et al. (2017) isolated seven compounds from the endophyte *Treptomyces* sp. OUCMDZ-3434 from green alga *Enteromorpha prolifera* (*Ulva intestinalis*) among which three, viz., ailupemycin J, R-, and S-wailupemycin K and 5-deoxyenterocin showed moderate anti-H1N1 activity.

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Table 2. The chemical nature and activity potential of bioactive compounds isolated from fungal endosymbionts of algae.

Fungus	Compound	Activity	References
<i>Apiospora montagnei</i>	Myrocin A, Apiosporic acid	Anticancer	Klemke et al. 2004
<i>Acremonium</i> sp.	Hydroquinone, Diterpene	Antioxidant	Abdel-Lateff et al. 2002
<i>Aspergillus</i> sp.	Flavus 2-Pyrone derivatives	cAMP production	Lin et al. 2008
<i>Aspergillus niger</i>	Isopyrophen, Aspergillusol, Pyrophen	Anticancer	Flewelling et al. 2015
<i>Aspergillus niger</i>	Diels–Alder adduct of asteroid and maleimide	Not mentioned	Zhang et al. 2007a
<i>Aspergillus niger</i>	Naphthoquinoneimine, Sphingolipids	Antifungal	Zhang et al. 2007b,c
<i>Aspergillus ochraceus</i>	7-nor-gosterolide, 3b,11a-dihydroxyergosta-8,24(28)-dien-7-one	Anticancer	Cui et al. 2010
<i>Aspergillus oryzae</i>	Indoloditerpenes derivatives	Antibiotic	Qiao et al. 2010
<i>Aspergillus terreus</i>	Chiral dipyrrolobenzoquinone derivatives	UV-A protection	Lee et al. 2003
<i>Aspergillus versicolor</i>	Siderin, Arugosin C, Vericulanol	Inhibition of hepatitis C virus	Jeewon et al. 2019
<i>Aspergillus versicolor</i>	Sesquiterpenoid-nitrobenzoyl esters	Anti-tumour	Belofsky et al. 1998

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<i>Aspergillus wentii</i>	Aspewentin A-C	Anticancer	Miao et al. 2012
<i>Beauveria felina</i>	Cyclodepsipeptides	Antimycobacterial, Antibacterial, Antifungal, Cytotoxic	Vita-Marques et al. 2008; Vijayakumari & Raj 2019
<i>Botrytis</i> sp.	Cyclopentenone derivatives	Not mentioned	Li et al. 2007
<i>Cadophora malorum</i>	New hydroxylated sclerosporin derivatives	Inhibition of fat deposition in cells	Almeida et al. 2010
<i>Candida railenensis</i>	Silicic acid, Diethyl bis(trimethylsilyl) ester	Antimicrobial	Juliet et al. 2018
<i>Chaetomium globosum</i>	Cytoglobosins A-F	Anticancer	Cui et al. 2010
<i>Chaetomium globosum</i>	Benzaldehyde and cytochalasin derivative	Antioxidant, Antitumour	Wang et al. 2006; Cui et al. 2010
<i>Coniothyrium cereale</i>	New phenalenone derivatives	Antibiotic, Inhibitor of human leukocyte elastase	Elsebai et al. 2011
<i>Curvularia</i> sp.	New macrolides	Antimicrobial	Dai et al. 2010
<i>Cystobasidium minutum</i>	Fungal P450, CYP53B1, a benzoate - <i>p</i> -hydroxylase, Phenol,2,4- bis(1,1-dimethylethyl)	Stereo and regiospecific hydroxylation of nonactivated C–H bonds, Antioxidant	Theron et al. 2019
<i>Drechslera</i>	10 new sesquiterpenoids	Antimalarial	Osterhage et al. 2002

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<i>dematioidea</i>			
<i>Emericella nidulans</i> <i>var. acristata</i>	Prenylated polyketides	Not mentioned	Kralj et al. 2006
<i>Exophiala oligosperma</i>	Phenoxynaphthalene	Not mentioned	Li et al. 2011
<i>Fusarium</i> sp.	Cyclic tetrapeptide	Anticancer	Ebel 2006
<i>Geniculosporium</i> sp.	11 new tricyclic sesquiterpenes	Antimicrobial	Krohn et al. 2005
<i>Grammothele fuligo</i>	Amylase and ligninolytic enzymes, Hexanedioic acid-bis-(2-ethylhexyl) ester.	Plasticizer derivative, Antimicrobial, Antioxidant	Prasher & Chauhan 2013; Naidu et al. 2017
<i>Myrothecium</i> sp.	Cyclopentenone derivatives	Tyrosinase inhibition	Li et al. 2005
<i>Penicillium chrysogenum</i>	Polyketide, Glycerol derivatives	Antifungal	Gao et al. 2011
<i>Penicillium citrinum</i>	Alkaloid	Anticancer	Tsuda et al. 2004
<i>Penicillium</i> sp.	Decalactones	Not mentioned	Bugni et al. 2004
<i>Pseudoanguillospora</i> sp.	New isochromans	Antimicrobial	Kock et al. 2009
<i>Rigidoporus vinctus</i>	Alcohol dehydrogenase (RvADH), 2-Ethylacridine and Butylated Hydroxytoluene	Antimicrobial, Antioxidant	Turcotte & Saheb 1978; Juliet et al. 2018; Vijayakumari & Raj 2019

4.2. Antioxidant activities

A variety of antioxidants are synthesized by the endophytes to prevent the light and desiccation stress in the algal hosts. These compounds have reactive oxygen species (ROS) scavenging potential with application in human healthcare. The marine fungus *Penicillium* sp. produces polysaccharides, which show significant antioxidant properties against superoxide and hydroxyl radicals (Mayer et al. 2013). An important algicolous marine fungus *Curvularia tuberculata* exhibited good antioxidant properties with 62.15% of inhibition in total reducing power assay and 11.69% of inhibition in hydroxyl radical scavenging assay (Venkatchalam et al. 2011).

Penicillium roqueforti, *Aspergillus candidus*, *Mortierella* sp., and *Emericella falconensis* are known to produce natural antioxidants. *Acremonium* sp. produced two novel hydroquinone derivatives, which showed significant ROS scavenging activity (Abdel-Lateff et al. 2004). The marine fungus *Halorosellinia oceanica* produced a new sesquiterpenoid that displayed a unique mechanism of bio-oxidation (Pan et al. 2008). Moderate radical scavenging activity was also observed with chaetopyranin, isotetrahydroauroglauclin and erythroglauclin of endophytic fungus *Chaetomium globosum* from *Polysiphonia urceolata* (Wang et al. 2006; Harikrishnan et al. 2021). Parasitenone was produced by the marine fungus *Aspergillus parasiticus* from the red alga *Carpopeltis cornea* and showed potent free radical scavenging activity (Abdel-Lateff et al. 2004). Additionally, the antioxidant activity of phenolic compounds from the marine algae *Halimeda monile* and *Porphyra haitanensis* indicate the possible sources for isolation of metabolites from endophytes (Mayer et al. 2013).

4.3. Industrial importance

Bioactive compounds produced by endophytes may have an ultimate application in industries. The potent antimicrobial and antioxidant activities along with significant potential to be used as anti-cancer drugs have opened the avenues for upscaling the processes to use them in industries. Apart from the secondary metabolites, these fungi have also been extensively studied for other alternate products like pigments, enzymes, value added metabolites, etc. *Cystoblastidium minutum* has been found to possess high carotene productivity (Dhaliwal and Chandra, 2015; Yurkov et al. 2015). Similarly, the ability of *Grammothele fuligo* to secrete amylase and ligninolytic enzymes has been well documented (Prasher & Chauhan 2013; Naidu et al. 2017). Alcohol

dehydrogenase (RvADH) was isolated and characterized from *R. vinctus* (Ken et al. 2016).

Some of the isolated endophytic fungi and their products have significant application in commercial industries. Hexanedioic acid-bis-(2-ethylhexyl) ester, found in the crude extract of *G. fuligo* BA212, is a plasticizer derivative and is very rarely reported from natural sources (Elleuch et al. 2010). Different strains of *P. kudriavzevii* possess potential probiotic activity and may be important in indigenous fermented food production (Greppi et al. 2017). *C. minutum* was found to produce an exemplary fungal P450, CYP53B1, a benzoate *para* hydroxylase, capable of catalysing the stereo and regio- specific hydroxylation of non activated C–H bonds (Theron et al. 2019). The ability of *P. kudriavzevii* in synthesis of ZnO nanoparticles through green method of synthesis was also explored (Moghaddam et al. 2017; Harikrishnan et al. 2021).

4.4. Growth promotion and defense

Endophytic fungi are able to promote the growth of their algal hosts (Bilal et al. 2018). Endophytes provide a variety of defense systems to the host such as reducing herbivory levels and increasing resistance to pathogens and pests (Bamisile et al. 2018). Endophytic fungi increase the resilience of host from extreme marine environmental conditions such as desiccation and drought, particularly during low tides when intertidal macroalgae are exposed for 8 hrs (Wicklow et al. 2005). The ability to survive in a high-stress environment is one of the factors that allows endophytic fungi to have a high degree of resistance and tolerance to extreme environmental changes (Waqas et al. 2015). Moreover, the endophytic fungi colonised in macroalgal thallus have the ability to mimic and improve the quality of copied metabolite compounds produced by its host (Radi & Štrukelj 2012). In addition, endophytic fungi help the host in terms of nutrient absorption thereby aiding to their rapid growth even under nutrient deplete conditions (Suryanarayana 2012). The presence of antimicrobial compounds, 2-Ethylacridine and Silicic acid, diethyl bis(trimethylsilyl) ester in GC chromatogram of *Rigidoporus vinctus* BT-GA2 and *Candida railenensis* BT-GAAB1, respectively have shown that the endophytes enhance the chances of growth of the host through induction of resistance to stresses (Juliet et al. 2018; Vijayakumari & Raj 2019).

5. Conclusion

The diversity, physiology and application potential of the algal endophytes, both fungi, bacteria and other microbes, are the least explored areas, compared to the extent of work done on the endophytes of higher plants. The search for potential drugs derived from marine algae should continue to tap more natural sources of medicinal compounds. Algae-derived endophytic fungi have the ability to produce similar compounds as that of their hosts as well as to induce the host to enhance the production of such compounds. Consequently the endophyte harboured algae have more concentration of the chemicals than of the non-harboured ones. Other bioactive compounds are also produced by the endosymbionts, which have been the focus of interest leading to production of important drugs.

This chapter has highlighted the achievements made in exploration and use of algal endophytic fungi indicating the possibilities for exploiting them for the production of a diverse type of bioactive compounds. There is great opportunity to find reliable and novel pharmaceutical leads in endophytic fungi of algal origin, which could be used for human welfare. Many studies have shown that marine organisms represent a potential platform for future pharmaceutical development but considering the vast diversity of the marine macrophytes, the data available on the endophytic association seem to be only a portion. There is a need to cover new areas for the identification and culture of endophytes for their beneficial use, since the endophytic associations with algal hosts are greatly determined by the habitat conditions. However, the sustainable use of endophytic fungi to extract potential drugs for medical use need more extensive study. There is also a need to optimize culture conditions of these fungi to successfully grow them in vitro and enable them to produce specific metabolites.

Acknowledgements

The authors thank The Head of the Department for enrolling SM and BBS to Ph. D. programme. Sanction of JRF to BBS by CSIR, New Delhi under CSIR-NET, and grant of FIST by DST, Govt. of India, New Delhi to the Department of Botany are highly acknowledged.

6. References

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Access this Chapter in Online	
	Subject: Endophytes
Quick Response Code	
DOI: 10.22192/enmpgp.2021	

How to cite this Chapter:

Smrutirekha Mishra, Barsha B. Swain and Pradipta K. Mohapatra. (2021). Fungal endosymbionts in algae: Ecology and application. Sonali Priyadarshini, S. Panigrahi and C. C. Rath. (Eds), *Endophytes: Novel Microorganisms for Plant Growth Promotion*. India: Darshan Publishers. pp: 92-122.

Overview on Endophytic Microorganisms and Host Interaction

Amanda K Ekanayake¹, Harshitha C K¹, Neha Gupta¹,
Sheeba E.²

¹Post Graduate Student, Department of Microbiology,
Centre for Research and PG Studies, Indian Academy Degree College -
Autonomous, Hennur Cross, Bengaluru, Karnataka, India – 560043

²Director, Rashya Centre for Learning, Peringannur Post, Peringode,
Palakkad District, Kerala – 679535

E mail: sheeba.elavalli@gmail.com

Introduction

Endophyte is a broad term enough to accommodate almost any microorganism which thrives within a plant host. Endophytic microbes fall into several identifiable classes often in relation to their plant organ source, which includes fungal endophytes of lichens, galls and cysts, prokaryotic endophytes of plants which includes endophytic bacteria and actinomycetes, fungal endophytes of dicots, roots, xylem, other systemic fungal endophytes (Stone et al., 2000, Bills et al., 2004). Perhaps some microorganisms appear to constantly invade host tissue by utilizing enzymes such as cellulase, for invading wounds of plants in specific circumstances (Correll et al., 1988). Microorganisms constitute a better source of bioactive secondary metabolites exhibiting a diverse range of biological functions like immune-suppressive, antibiotics, anticancer, insecticidal, plant growth promoting agents. Endophytes are well known for their ability to promote compounds that play a role in the growth of the host organisms like plants (Eid et al., 2019, Kahlil et al., 2021). Certain endophytic microorganisms are capable of producing plant growth factors or hormones such as indole acetic acid, utilizing precursor molecules like tryptophan. They are capable of producing certain compounds which aids in the plant growth process, promoting host plant abiotic & biotic stress tolerance, (Fig - 1) (Fouda et al., 2021; Wu et al; 2021).

Evolution

Any microorganism living within a host tissue is referred to as an endophyte, which was initially described in the year 1866 by De Bary (Bary, 1866). Endophytes have adapted to their unique microhabitat through

evolutionary divergence, where certain species incorporate the host genome into its own DNA, over the course of their prolonged co-evolution with the plant host. This could be explained by the process of phytochemical synthesis occurring in certain endophytic organisms, which initially can be seen in plants (Germaine et al; 2004). Transmission of endophytic fungi and bacteria can be distinguished into two routes as, vertical transmission which involves the passage of the systemic fungus from plant to progeny via host seeds, whereas horizontal transmission involves sexual or asexual spore transfer. Endophytic microorganisms, according to co - evolution principle, boost host plant tolerance to adversities through the synthesis of bioactive metabolites (Saikkonen et al., 2004; Frank et al; 2017).

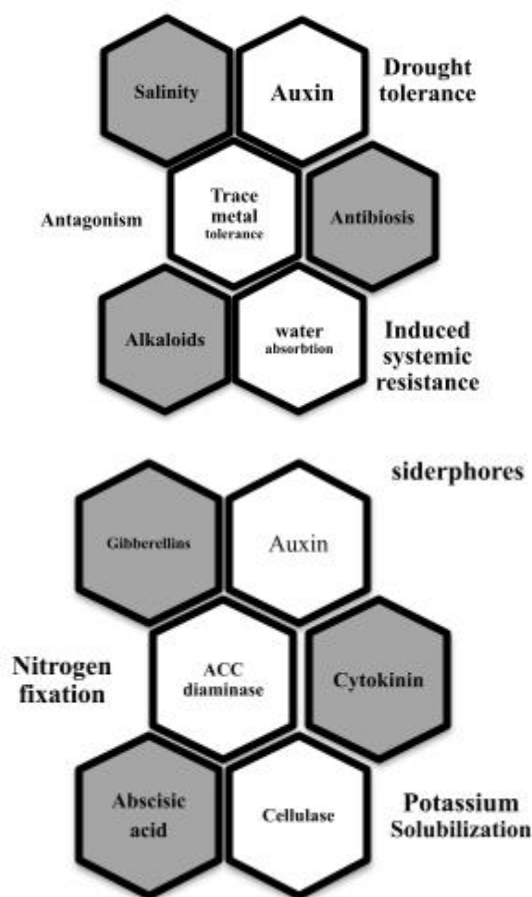


Fig 1: Applications of endophytes

Distribution

Distribution of endophytic microorganisms can be found throughout the plant bodies in a large variety of plants (Table 1, 2 & 3). Based on their pattern of distribution they can be categorized as obligate endophytes, facultative endophytes or passive endophytes (Hardoim et al; 2015). Endophytes are specific based on host, location, genotype, properties of soil. Identifying different endophytic microorganisms and understanding the potential of those organisms in promoting the growth of particular plants is an essential process. Therefore, identification of growth promoting properties of endophytes allow us to recognize novel endophytes possessing similar properties (Kumar et al; 2020). According to several reports, there are different plants and plant tissues that habitat native endophytic bacteria. Each plant niche provides a unique environment, hence, bacterial endophytes possess different specialization, functions, competence and adaptations (Lodewyckx et al; 2002; Walitang et al; 2017). Fungal endophytes dwell on plant tissues like fruits, stems, leaves, branches and fruits (Omomowo & Babalola, 2019). These endophytes colonize in the same niche as plant pathogens in the host plant. Based on several studies conducted, the bacteria which belong to the taxa Actinobacteria, Proteobacteria, Bacteroidetes and Firmicutes are most dominating colonizers as endophytes in different sections of plants (Agarwal et al; 2020). Endophytic actinomycetes can be found in different parts of the plant host such as., roots, stem, leaves, flowers and petioles. Most dominating Actinomycetes group found is *Streptomyces*, followed by *Microbacterium*, *Brevibacterium* and *Leifsonia* (Passari et al; 2015).

Table 1:Endophytic Bacteria and their distribution in plants

Endophytic Bacteria	Plant Host	References
<i>Bacillus amyloliquefaciens</i>	<i>Pennisetum glaucum</i> (Pearl Millet)	Kushwaha et al., (2020)
<i>Bacillus amyloliquefaciens</i> , <i>Bacillus subtilis</i> , <i>Bacillus tequilensis</i>	<i>Citrus spp.</i>	Daungfu, Youpensuk & Lumyong., (2019)

<i>Bacillus cereus</i> , <i>Bacillus subtilis</i> , <i>Enterobacter cloacae</i> , <i>Enterobacter tabaci</i> , <i>Bacillus stratosphericus</i> , <i>Bacillus pumilus</i> , <i>Leclercia adecarboxylata</i> , <i>Klebsiella pneumoniae</i> , <i>Enterobacter asburiae</i> , <i>Bacillus thermophilus</i> , <i>Bacillus xiamenensis</i> , <i>Xanthomonas sacchari</i> , <i>Bacillus elezensis</i>	<i>Oryza sativa</i> L (Rice)	Kumar et al., (2020)
<i>Pantoea dispersa</i> , <i>Pseudomonas</i> sp, <i>Enterobacter</i> sp.	<i>Saccharum ocinarum</i> (Sugar cane)	De Silva et al., (2019)

Table 2: Endophytic Fungi and their distribution in plants

Endophytic Fungi	Plant Host	References
<i>Aspergillus awamori</i>	<i>Withania somnifera</i> (Ashwagandha/Winter cherry)	Mehmood et al., (2019)
<i>Aspergillus fumigatus</i> , <i>Fusarium proliferatum</i>	<i>Oxalis corniculata</i> (Creeping Woodsorrel)	Bilal et al., (2018)
<i>Penicillium aurantiogriseum</i> , <i>Alternaria alternate</i>	<i>Triticum aestivum</i> (Wheat)	Ripa et al., (2019)

<i>Porostereum spadiceum</i>	<i>Glycine max</i> (Soybean)	Hamayun et al., (2017)
<i>Yarrowia lipolytica</i>	<i>Euphorbia milii</i> L. (Christ Plant/Crown of Thorns)	Gul Jan et al., (2019)

Table 3: Endophytic Actinomycetes and their distribution in plants

Endophytic Actinomycetes	Plant Host	References
<i>Streptomyces</i> sp.	<i>Zingiber officinale</i> (Ginger)	Taechowisan et al., (2003)
<i>Streptomyces.</i> , <i>Nocardia</i> sp., <i>Micromonospora</i> sp., <i>Microbispora</i> sp., <i>Nocardiopsis</i> sp.	<i>Citrus reticulata</i> L. (Mandarin Orange)	Tanvir, Sheikh & Javeed., (2019)
<i>Micromonospora</i> sp., <i>Streptomyces viridis</i> , <i>Streptomyces albosporus</i> , <i>Streptomyces cinereus</i> , <i>Micromonospora</i> sp., <i>Saccharopolyspora</i> sp.	<i>Aloe barbadensis miller</i> (Aloe vera)	Tanvir, Sheikh & Javeed., (2019)
<i>Streptomyces</i> sp., <i>Streptosporangium</i> sp., <i>Microbispora.</i> , <i>Streptoverticillium</i> sp., <i>Sacchromonospora</i> sp., and <i>Nocardia</i> sp.	<i>Azadirachta indica</i> A. Juss (Neem)	Verma et al., (2009)

Host-Endophytes Interaction

Microorganisms can be found in both plants and animals. Bacteria in the gut are important for development of overall immunity in humans. In a similar manner plant microbes are also capable of inducing plant host immunity against pathogenic microorganisms (Nogueira et al., 2001). Root exudates, a type of organic compounds which function as signaling molecules, benefit microorganisms on roots and in the rhizosphere. These compounds allow for communication among the host plants and the microorganisms, which can join the plant as endophytes that do not really impact the plant, instead form a mutualistic relationship (Hallmann et al., 1997). It remains unresolved whether plants benefited more from the endophyte or whether the endophytes become more beneficial to the host. It is not yet known which microbial population, either endophytic or rhizospheric microorganisms, promote the growth of host plants (Rosenblueth et al., 2006).

Microorganisms can boost growth through the production of phytohormones, nitrogen fixation, and manufacturing biocontrol agents like antibacterial or antifungal components against plant pathogens, nutritional contestability, siderophore assembly, and enhancing host immune response. The understanding of the mechanisms that promote plant growth will aid in the selection of species and situations that result in increased plant advantages (Sessitsch et al., 2002). Various interactions have been developed between endophytic fungi and their host plants through a significant duration of evolutionary history and co-existence through a specific association termed as mutualism, antagonism (Jia et al., 2016). According to the data (Suryanarayanan et al., 2005), various environmental factors like temperature, vegetation, humidity, geographic position, have substantial impact on the density variation of endophytic fungus.

As endophyte dwelling inside the host is also in advantageous side, as the influence distribution ranges of host plants under few specific environmental conditions, which in turn determines the species of endophytes and their growth, spore germination, metabolism throughout the life cycle and reproduction (Dia et al., 2003). Temperature, humidity, and soil nutrition levels were all key factors in determining the types and amounts of secondary metabolites produced by the host plants, which in turn affected the population structure of the endophytic fungi. For particular, under conditions of low mean and high mean annual sunlight hour humidity, the host plants would produce more nutrients suited for the endophytic fungi's colonization, spread and reproduction, (Wu et al., 2013). In contrast, only selected types of host species

could thrive well under freezing temperature, oxygen concentration, improper rates of respiration and pH value. Thus, only a finite number of distinct endophytes could proliferate in the respective host plants, given in a degree of geographic specificity in endophyte community structure (Jiang et al., 2010).

Phytohormones synthesis like Indole-3-Acetic Acid (IAA) one among plant hormones produced from an endophytic fungi present in *Phyllanthus niruri* plant was identified as *Fusarium oxysporum* (Junaidi et al., 2017), whose function in enhancing plant growth that promotes cellular proliferation by altering various circumstances in the cell, such as boosting osmotic contents, decreasing membrane stress, increasing water permeability, enhancing and stimulating cell wall production, protein synthesis (Mohite et al., 2003). Biostimulants are a nutrition source alternative to chemical fertilizers in the cultivation of food crops. A heterotrophic bacteria that uses organic materials as a carbon source and an energy source from plants, like *Azotobacter salinestris*, fixes nitrogen in the presence of 1.0 to 1.5 percent Sodium chloride (Page et al., 1991). Other strains of *Azotobacter* like H12 improved fixation of atmospheric nitrogen, as well as isolates doubled IAA output on 0.3 percent salt media (Paul et al., 2014). The implementation of novel antimicrobial compounds from endophytes is a key option for combating rising levels of antibiotic resistance. A significant number of antimicrobial substances identified from endophytes, including phenols, peptides, quinines, steroids, alkaloids, terpenoids, and flavonoids are structural classes of classified group. The bioactive substance from endophyte *Xylaria* sp. YX-28, 7-amino-4-methylcoumarin was recovered from extracts of the *Ginkgo biloba* plant. These substances exhibited significant inhibitory activity against *Escherichia coli*, *Salmonella typhi*, *Yersinia* sp., *Candida albicans*, *Aspergillus niger*, *Staphylococcus aureus*, *Aeromonas hydrophila*, many other food spoilage and food-borne microorganisms (Liu et al., 2008).

The makeup of a plant's root exudates plays an important role in defining the type of microbe that can be linked with it. As a result, the ability of endophytic bacteria to utilize the exudates produced by plant roots as a source of energy is critical to their relationship with plants (Andreozzi et al., 2019; Kandel et al., 2017). Endophytic microbes contribute to plant fitness through a variety of processes, using diverse ways to achieve their goals, which are mainly categorized as direct and indirect mechanisms of action (Fadiji et al., 2020).

Table 4: List of criteria for host endophytes interaction

Characteristics	Endophytes interactions
Infection mode and site	<ul style="list-style-type: none">) Active with enzymes or vectors, such as insects.) Passive through wounds and other tissue breaksStomata, cell walls, and wounds are all active mechanisms.
Food source	<ul style="list-style-type: none">) Host metabolic byproducts, dead cortex cells, and plant detritus.) Lesion present on host, dead frontal cells, including reserve substance in the spores
Tissue invasion	<ul style="list-style-type: none">) The most communal type is intercellular tissue however, vascular tissue exists as well specially in fungal endophytes.
Association	<ul style="list-style-type: none">) Intrinsic pathogenicity) Commensalism) Mutualism
Endophyte key advantages	<ul style="list-style-type: none">) Passive transfer hosts via vectors.) Consistent source of nutrients, protection from environmental challenges.) Nutrition to reproduce and colonization.
Host key advantages	<ul style="list-style-type: none">) Better phytohormones, N-fixation.) Given a way to water, minerals and nutrients.) Production of metabolites hostile to predators and antagonists.) Improved susceptibility

Direct Host-Endophyte form of Action

Despite the fact that certain research has revealed new methods by which endophytes reduce pathogen effects, current understanding on endophytes, pathogens, and plant regulation still seems to be incomplete. Endophytes produce antibiotics directly, which aid in the suppression of infections in the direct method. Direct endophyte-pathogen interactions, on the other hand, are complicated and sensitive to species-specific antagonism (Arnold et al., 2003).

Lytic enzyme production

Most bacteria release lytic enzymes that hydrolyze polymers. A total of 1,350 molecules can be released for lysis of, including chitin, hemicellulose, DNA, proteins, and cellulose (Tripathi et al., 2008). Endophytes create a slew of enzymes that aid in the breakdown or catalyze cell wall of the plant, allowing them to populate the plant's exterior.

Siderophore production

Certain microorganisms produce siderophores as a result of iron deficiency whereas these siderophores are high affinity molecules, which are able to capture iron molecules and chelate them, providing iron for plants (Loaces et al., 2011; Yadav et al., 2018). Chrome Azurol S (CAS) media can be used for the screening process of siderophore producing endophytic bacteria (Schwyn & Neilands, 1987; Afridi et al., 2019).

Competition with pathogens

Endophytic microorganisms compete with pathogenic microorganisms for the survival process throughout the host (Martinuz et al., 2012). Endophytic distribution throughout the host plants can be seen in a systematic distribution pattern, to inhibit the entry of pathogenic organisms. Also certain endophytes are able to produce metabolites for suppression of the growth of pathogenic flora (Arnold et al., 2003; Fadiji & Babalola, 2020).

Indirect Host-Endophyte form of Action

Endophytes boost plant survival instincts by generating bioactive constituents and increasing resistance (Gouda et al., 2016). Endophytes have been shown to create a variety of bioactive components in a single plant or microbe, making them an ideal source of pharmaceuticals for the treatment of many diseases and with potential applications in agricultural, medical, food, and cosmetics sectors (Godstime et al., 2014).

Plant resistance induction and secondary metabolite production stimulation

Existence of endophytic organisms, with the host plant induce building of host plant resistance against pathogenic infections in two methods as, induced systemic and systemic acquired resistances. Common endophytes which are responsible for stimulation of ISR and SAR are *Pseudomonas* spp., *Trichoderma asperellum*, *Serratia* spp. etc. (Van Loon, Bakker & Pieterse, 1998; Ongena et al., 2004; Shores, Yedidia & Chet, 2005; Fadiji & Babalola,

2020). Similar to the process of resistance development, certain endophytes are capable of increasing secondary metabolite production by the host plants. Among these secondary metabolites of plants are antimicrobial substances and enzymes etc. (Bourgau et al., 2001; Gao, Dai, & Liu, 2010). Endophytic organisms are the novel organisms that provide a chance for the innovation of drugs and discovery of agrochemicals. It can be used in the following mentioned applications.

Antimicrobial agents: Fungal endophytes can be used as another source of antimicrobial compounds. Endophytic fungus contains antimicrobial compounds such as Clavatul, guignardic acid, viridicatol, chaetomugilin D, altersolanol A, javanicin, colletotric acid, enfumafungin, 2- hydroxy-6 methyl benzoic acid, jesterone, hypericin, xylarenone B, pastacin, fusapyridon A, etc. Therefore, endophytic fungi are suitable organisms for the production or extraction of antibacterial, antiprotozoal, antifungal and antiviral compounds (Strobel & Daisy, 2003; Adeleke & Babalola, 2021).

Antitumor agents: Endophytic fungus possess bioactive compounds which show anti-cancer activity and also an action mechanism in inhibiting carcinogenesis. Bioactive compounds which show such activities are Paclitaxel, Vinblastine, Vineristine, Podophyllotoxin, Camptothecin, Piperine, Cytochalasins etc. For example, *Xylaria* sp. an endophytic fungus that colonizes in the *Ficus carica* plant can produce cytochalasins that show antitumor activity (Banyal, et al., 2021).

Antioxidants: Endophytes can produce alkaloids, flavonoids, peptides, quinines, steroids, phenols, and terpenoids. These all-bioactive compounds have antioxidant activity hence, can be used as antioxidants (Atiphasaworn, et al., 2017).

Insecticidal activities: Endophytic microorganisms are not commonly used as a source of insecticidal factors; therefore, it can be used for the natural insecticides development and can represent a new field of study. For instance, *Penicillium* sp. presents insecticidal activity opposed to diamond backed moth (Shi et al., 2013).

Antidiabetic agents: According to several studies, fungal endophytes can exhibit anti diabetic activity. For example, *Nigrospora oryzae* an endophytic fungus exhibits strong anti-diabetic activities and therefore, can be used as another source of novel compounds for the diabetes management (Uzor., Osadebe & Nwodo, 2017).

Immunosuppressive compounds: Immunosuppressive medicines are mainly used to avoid the rejection of allograft in transplant patients. As an example, *Fusarium subglutinans*, an endophytic fungus that colonizes in *Tripterygium wilfordii* plant, can biosynthesize immunosuppressives (Strobel & Daisy, 2003).

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Access this Chapter in Online	
	Subject: Microbiology
Quick Response Code	
DOI: 10.22192/enmpgp.2021	

How to cite this Chapter:

Amanda K Ekanayake, Harshitha C K, Neha Gupta, Sheeba E. (2021). Overview on Endophytic Microorganisms and Host Interaction. Sonali Priyadarshini, S. Panigrahi and C. C. Rath. (Eds), *Endophytes: Novel Microorganisms for Plant Growth Promotion*. India: Darshan Publishers. pp: 123-141.

The Fungal Endophyte–Plant Interactions: Scope in Sustainable Agriculture

Anurag Yadav¹, Kusum Yadav² and Rumana Ahmad³

¹ Department of Microbiology, College of Basic Science & Humanities,
S.D. Agricultural University, S.K. Nagar, Dist. Banaskantha,
Gujarat-385506, India.

E-mail: anuragyadav123@gmail.com

² Department of Biochemistry, University of Lucknow, Lucknow,
Uttar Pradesh-226007, India

³ Department of Biochemistry, Era University, Lucknow,
Uttar Pradesh-226003, India

1. Introduction

The term ‘endophyte’ was proposed by De Bary (1866) for the organisms that remain present inside plant tissues without causing any disease symptoms. Several species of bacterial, fungal and viral endophytes are known to colonize plant tissues. Their presence is considered ubiquitous in the plant kingdom. However, the endophyte-plant association is complex and not fully understood.

Fungi are the predominant members of the endophytic community. Being filamentous, fungal endophytes (FEs) more intensively impact plant growth and metabolism. Endophyte fungi live at least some part of their life cycle inside plant tissues. Millions of different fungal species are surviving on earth, most of which have not been identified. These fungi may be common saprophytes, animal or human pathogens, phytopathogens, endophytes or mycorrhizal.

Contrary to mycorrhizal fungi, the FEs grow inside plant tissues (Stone et al., 2004). Most of the time, such associations are symbiotic. Most endophytes enter the plant system through foliage, roots, stems, and bark and could also horizontally transmit through spores (Faeth & Fagan, 2002), forming a ‘constitutive’ or ‘inducible’ endophytism. The former involves endophyte-infected plants that transfer the infection vertically via seeds. The latter includes several other fungi that colonize host tissues (Carroll, 1988).

The roots of more than 90% of flowering plants harbor the largest pool of FEs in the plant body. The FEs are considered more diverse than free-living fungi in the environment. Furthermore, FEs can live inside the plant for the entire lifespan (from seed to seed), suggesting their essential role in plant biology. Indeed, FEs have been recognized for promoting plant growth and for disseminating many defensive and protective functions. The four classes of endophytic fungi include 1) clavicipitaceous, 2) non-clavicipitaceous, 3) fungi growing exclusively in plant above-ground tissues and 4) dark septate endophytes belonging to Ascomycota and non-mycorrhizal members of Sebaciniales, Basidiomycota (Andrade-Linares & Franken, 2013; Rodriguez et al., 2009).

2. Fungal endophyte species diversity and interaction with other organisms

The FEs appear to be ubiquitously symbiotic within the plant ecosystem. They are a diverse group of fungi that also include some mycorrhizal fungi. The fungal diversity of this group has direct implications on plant communities, thus providing abiotic and biotic stress tolerance, enhancement in biomass, change in plant water utilization, etc., to the host. The Ascomycetes family, Clavicipitaceae belongs to most of such endophytes (Gutierrez et al., 2012).

In the soil surrounding the root system, wide ranges of microbiome exist that interact with each other and plants through various levels of interactions (Fig. 1). Fig. 2 describes several possible types of interaction between FEs, plants and pathogens.

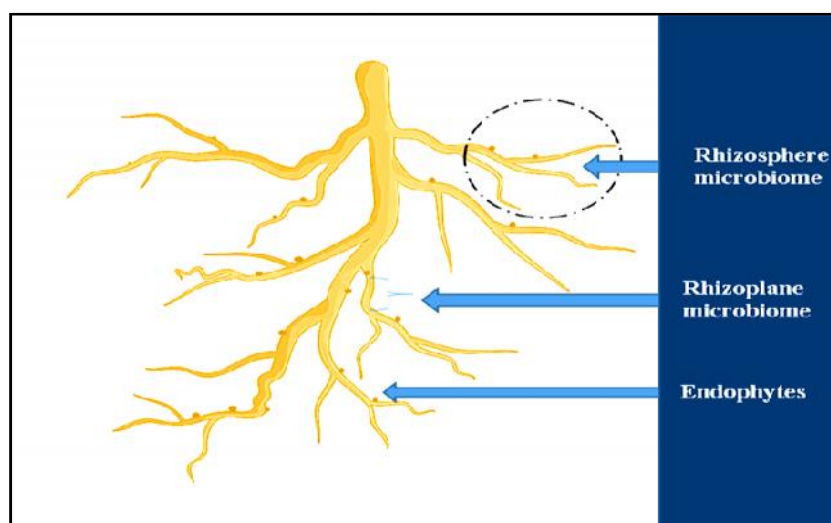


Fig. 1: Types of microbiomes present in the root system

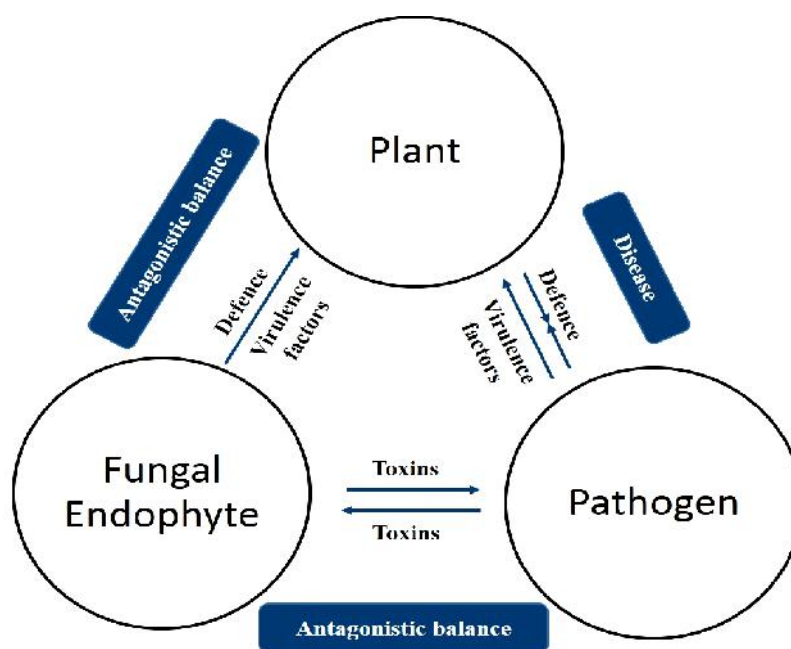


Fig. 2: Various types of known interactions between plant, fungal endophyte and pathogen

2.1 Interaction with the plants

The relationship between endophytes and hosts is complex and temporally variable. The FEs alters the interaction of the plant with the environment to modulate their interplay with phytopathogens (Zabalgogea, 2008). The FEs grows inside plant roots, stems, or leaves and sporulates in host tissues to cause senescence. The endophytic infection spread horizontally from plant to plant or vertically through seeds. The infection starts through mechanical abrasions, tears or wounds in plant roots during or after germination. The FEs infection through aerial plant parts is although unnatural but may begin through stomatal and other natural openings. The utility of hydrolytic enzymes as portals of entry in roots and leaves is also considerable. The internal environment ensures sufficient nutrition for such microbes as intercellular spaces of plant cells are rich in organic and inorganic nutrients.

The FEs face little competition from other microorganisms inside the plant as the endosphere is a protected niche. Plants defend themselves from foreign invaders through systematic acquired resistance (SAR) and induced systemic resistance (ISR). The former is pathogen-induced resistance, mediated by the salicylic acid pathway that causes accumulation of pathogenesis-related (PR) proteins, while the latter is induced by rhizobacteria through jasmonic acid or ethylene pathway. The PR proteins are mostly hydrolytic enzymes that lyse the invading cells. The enzymes include chitinases and α -1,3-glucanases (Fukuda & Shinshi, 1994) and pathogenesis-related genes. These enzymes maintain cellular boundaries by causing localized cell death of invaders. The degree to which plants defend themselves against endophytes is a matter of further research.

The FEs interact with plants to form beneficial symbiotic associations. Such fungi are not capable of causing the disease to the plant but are recognized as a valuable partner by the plant. Such interactions assist the plant by improving its ability to tolerate abiotic stress by enhancing resistance to pests, herbivores, or diseases. For example, *Fusarium oxysporum* f. sp. *lycopersici*, a fungal endophyte, has been shown to protect the tomato plant from disease and abiotic stress, such as drought, cold, high salinity or oxidation by the combination of several direct and indirect means (Mandal et al., 2009). Foliar application of *F. oxysporum* before pathogen challenge enhances the plant resistance to fungal disease in several ways (Mandal et al., 2009).

2.2 Interaction with grazing animals

Land grass remains infected with symbiotic endophytes and benefits from endophytic associations. Such associations result due to the secretion of anti-herbivorous alkaloids by endophytes. For example, the FEs *Neotyphodium* sp. and *Epichloë* sp. produce alkaloids that confer the plant with resistance to insects and grazing animals (Zhang et al., 2012). The discovery of toxic FEs arouses suspicion of their widespread toxic nature until the contrary is proved. Numerous health problems have been associated with animals grazing on tall fescue (*Festuca arundinacea* Schreb.) infected with fungal endophyte, *Acremonium coenophialum* (Read & Camp, 1986). The animals grazing on tall fescue suffers from fescue foot syndrome, associated with soreness and lameness of the feet; and summer syndrome, a state of weight loss, difficulty in breathing and elevated body temperatures. However, not all FEs are toxic to grazing animals (Cunningham, 1958).

2.3 Interaction with phytopathogenic fungi

Endophytic fungi produce several antibiotic compounds (Brady et al., 2000). Studies show in vitro inhibition of plant pathogenic fungi from endophyte cultures (Cho et al., 2007). Hyperparasitism is another ecological phenomenon that endophytes use to protect host plants. Hyperparasitic FEs directly attack pathogens and kill them or their propagules (Tripathi et al., 2008). The FEs hyperparasite phytopathogenic fungi by hyphal twisting, infiltration and by breaking down the bacterial cell wall by secreting lyase. Hyperparasitism of *Trichoderma* on *Rhizoctonia solani* is a well-known phenomenon applicable in biocontrol measures (Grosch et al., 2006). In addition, FEs control fungal phytopathogens through active predation, especially under nutrient scarcity. *Trichoderma* fungus secretes cell-wall hydrolyzing enzymes to absorb nutrients from fungal pathogens (Benhamou & Chet, 1997).

2.4 Interaction with mycorrhizal fungi

Many FEs coexist with other microbial groups in the microbiome. Some endophytes may form mycorrhiza-like structures. The roots of the orchid, *Dendrobium nobile*, inoculated with an endophyte, *Leptontidium*, form structures similar to pelotons and improve plant growth through mycorrhizal interactions (Porras-Alfaro & Bayman, 2011). The root endophytes activate host specific metabolic pathways that facilitate the transfer of nutrients. For example, the external hyphae of *Piriformospora indica* in corn roots express a phosphate transporter [propylisopropyltryptamine (PiPT)] (Porras-Alfaro &

Bayman, 2011). It seems that FE and mycorrhizal fungal mechanism of interaction with the host is similar. Certain fungi evolved to become FEs by losing saprophytic traits and developed into mycorrhizal fungi by colonizing below-ground plant parts (Strullu-Derrien et al., 2018). However, there are some differences between FEs and mycorrhizal fungi in the context of fungal-dependent mechanisms that enable the plant-microbe consortia to survive under the challenge of toxic metals. For example, the FEs remain abundantly present in all plant tissues while mycorrhizal fungal growth remains restricted to roots.

2.5 Interaction with insects

Most fungi are soil-borne, form symbiotic associations with plants and may infect a range of insect hosts to transfer insect-based nitrogen. The FEs produce alkaloids like quinolones and isoquinolines (ergot, peramine, lolines and pyrrolizidines); amines and amides; indole derivatives; pyridines and quinazolines with insecticidal and host healing properties (Zhang et al., 2012). The FEs, through the active mycelial network, transports insect-derived nitrogen to plants. Several FEs have shown antimicrobial activity against various insect pests (Hu & Bidochka, 2021). Studies on several herbaceous plants have demonstrated that FEs, directly and indirectly, interact with herbivorous insects by secreting bioactive compounds or by modifying metabolites (Eberl et al., 2019). To date, most studies of tripartite interactions between fungi, plants, and insects were performed on short-lived annual agriculture crops against phytopathogens. Little is known about endophytic fungal colonization and interactions with woody perennials and insects. Also, our understanding of the interaction between FEs, woody plants and insect pests is incomplete (Eberl et al., 2019).

2.6 Interaction with nematodes

The nematodes are microscopic soil pathogens that feed on plant roots, stems, leaves, flowers, and seeds. Endophytes are gaining impetus in plant pathology as they confer resistance to plants against phytopathogens (Zabalgogezcoa, 2008). Sometimes endophytes remain restricted to certain plant parts. The FEs restrict pathogen entry through antibiosis or cause paralysis and lysis of nematodes. (Zabalgogezcoa, 2008). Some FEs attack, kill, paralyze, repel or disrupt nematode development by competing for resources in the microenvironment of the host cell (Schouten, 2016).

2.7 Interaction with bacteria

The antibacterial, antifungal and anti-nematicidal effects of FEs are well known (Wang et al., 2007). A study describes the association of 400 phylogenetically diverse endophyte bacteria with the common fungi. Such associations are widespread in plant microcosm than earlier thought (Hoffman & Arnold, 2010). FEs interact with bacterial endophytes by forming biofilms. However, such interactions are uncommon in the internal host environment due to physical barriers of tissues. In nature, the bacteria interact with fungal hyphae by secreting biofilms. Biofilm formation depends on cell density-based quorum sensing, which seems unusual in the limited cellular spaces (Bandara et al., 2006). In addition, the occurrence of bacterial and FE communities in the endosphere is governed by several physiological and genetic factors (Wemheuer et al., 2019).

2.8 Interaction with viruses

As the estimated number of fungal species ranges between 1.5-5.1 million, the number of FE viruses could supposedly be high. The experiment on *Lolium pretense* infected with *Neotyphodium* sp. showed lower barley yellow dwarf virus (BYDV) occurrence than endophyte-free plants. The endophyte controls aphid vector growth by secreting toxic fungal alkaloids inside plants causing lower BYDV spread (Lehtonen et al., 2006). Looking at their persistence, they may play a variety of roles to benefit their partners. The *Curvularia* thermal tolerance virus (CThTV) is the only known example of mutualism with plants and FEs. To survive temperature >50°C panic grass, *Dichanthelium lanuginosum* needs fungal endophyte, *Curvularia protuberata*. On the other hand, the fungus requires CThTV to confer heat tolerance to the plant and fungus (Roossinck, 2011). Multiplex mutualism between viruses-plant-endophytes must not be rare in nature. Although, such interactions are hard to detect. The knowledge accumulating in this field could be valuable in sustainable agriculture.

3. Agricultural applications of fungal endophytes

The role of endophytes in agriculture is a topic of extensive discussion. Some endophytes influence plant physiology and ecology by modifying their responses to biotic and abiotic stress. A ‘good’ endophyte enhances the productivity of plants in agricultural production. The diversity and frequency of FEs in crops suggest that many such fungi are the essential components for primary production in agricultural ecosystems.

The genotype of host plant species and culture media conditions determine the isolation of FEs. The FEs with potential host-specific beneficial effects must be selected from the wide range of host plants to maximize host-plant specificity. Successful endophyte-host plant colonization can then be enhanced or established through plant growing techniques. The seeds and seedlings should be thoroughly washed before inoculation to prevent surface fungal contamination. The endophytism or pathogenicity of several FEs is a plant-specific character. For example, *Verticillium dahliae* is an asymptomatic endophyte of mustard and barley but severe potato pathogen (Wheeler et al., 2019). Therefore, the selection of host-specific endophytes is a crucial step in crop improvement.

3.1 Extracellular enzymes production

The unique balance of chemical, physical and biological components (including microbial and enzymatic activities) helps maintain soil health. Enzymes are vital activators in life processes and play an essential role in soil health. Their action in the soil is mainly of microbial origin, derived from intracellular, cell-associated/free enzymes. Enzymes like amylase, arylsulphatase, -glucosidase, cellulase, chitinase, dehydrogenase, phosphatase, protease are vital soil components (Das & Varma, 1970). Outside the host, FEs and other microorganisms degrade soil biomass and recirculate nutrients in the ecosystem through hydrolytic enzymes like cellulases, laccases, pectinase, phosphatases, lipases, xylanases and proteinases. Inside the host, the FEs defend themselves and the host from pathogenic invasion by releasing such enzymes. The FE-based enzymes break down the pathogen-derived macromolecules like lignin, sugar-based polymers, proteins, organic phosphates and carbohydrates to utilize the broken macromolecular units by cellular transport for maintaining host symbiosis (Strong & Claus, 2011). Some FEs release 1-aminocyclopropane-1-carboxylate deaminase in plant tissues, which reduces drought, salinity, temperature, waterlogging, heavy metals, and pH induced stress by lowering plant ethylene levels (Glick, 2014).

In a study on banana plants infected with *Fusarium oxysporum* and treated with endophytic fungi like *Trichoderma reesei*, *Polyporus vinctus* and *Sphingobacterium tabacisoli*, the increased level of defense-related enzymes such as peroxidase, phenylalanine ammonia-lyase and polyphenol oxidase was observed (Savani et al., 2020). Endosphere study of four medicinal plants, viz. *Adhatoda vasica*, *Costus igneus*, *Coleus aromaticus* and *Lawsonia inermis* revealed the presence of 11 dominant endophytic fungi, namely, *Cladosporium cladosporioides*, *Curvularia brachyspora*, *C. verruciformis*, *Drechslera hawaiiensis*, *Colletotrichum carssipes*, *Colletotrichum falctum*, *Colletotrichum*

gleosporioides, *Lasiodiplodia theobromae*, *Nigrospora sphaerica*, *Phyllosticta* sp. and *Xylariales* sp. and the isolated endophytes produced extracellular enzymes like amylase, cellulase, laccase, lipase, protease at various levels (Amirita et al., 2012).

3.2 Secondary metabolite production

It is becoming increasingly important to explore novel and bioactive compounds for agrochemical use due to rising instances of pesticide resistance. Moreover, most of the currently used pesticides are xenobiotic. The novel fungal endophytes could specifically be explored for secondary metabolites due to their ubiquitous nature and wide host ranges. The potential of FE-based metabolite discovery is immense, looking at approximately 300,000 plant species that at least harbor one endophyte during their life span.

The FEs can make our modern agriculture system more sustainable by improving plant growth and yield by alleviating biotic and abiotic stress (Busby et al., 2016; Lugtenberg et al., 2016).

Endophytes possess several important compounds beneficial for plant health. Such chemicals fall under the range of alkaloids, terpenoids, steroids, isocoumarins and chromones, phenolics and volatile organic compounds (Kumar & Kaushik, 2013). The beneficial effects of FEs are shown in Table 1, and their modes of plant growth promotion are displayed in Fig. 3. The FE-derived metabolites could be of great importance in developing fungicidal biomolecules. Due to the endophytic nature of such fungi, the effect of such metabolites on phytopathogens and plants would be direct and intense.

Table 1: Beneficial effects of fungal endophytes on the host plants

Benefits	Mechanisms	References
Photosynthetic modulation) Chlorophyll content modification	(Sanchez-Azofeifa et al., 2012; Sarkar et al., 2021)
) Reduction in leaf vapour conductance	(Arnold & Engelbrecht, 2007)
) Influencing internal CO ₂ concentration & CO ₂ fixation in plants	(Harman et al., 2021; Harman & Uphoff, 2019; Monnet et al., 2001)
Nutrient uptake increase) Expansion of root development	(Zhang et al., 2016)
) Upregulated metabolism & transporter genes	(Su et al., 2019)
) Production of exolytic enzymes & metal chelators	(Deng & Cao, 2017; Oses-Pedraza et al., 2020)
Enhance biotic stress tolerance) Increased lamina density of leaves	(Khare et al., 2018)
) Influencing physiology of herbivorous insects	(Cosme et al., 2016; Fernandez-Conradi et al., 2018; Jaber & Vidal, 2010)
) Advancement in jasmonic & salicylic acid pathway	(Kou et al., 2021; Martínez-Medina et al., 2017)
Enhance abiotic stress tolerance) Increased efficiency of antioxidative system	(Fouda et al., 2020; Li et al., 2012)
) Regulation of phytohormone levels	(Bilal et al., 2018)
) Control of proline & flavonoid content	(Hamayun et al., 2018; Khan et al., 2013; Mona et al., 2017)

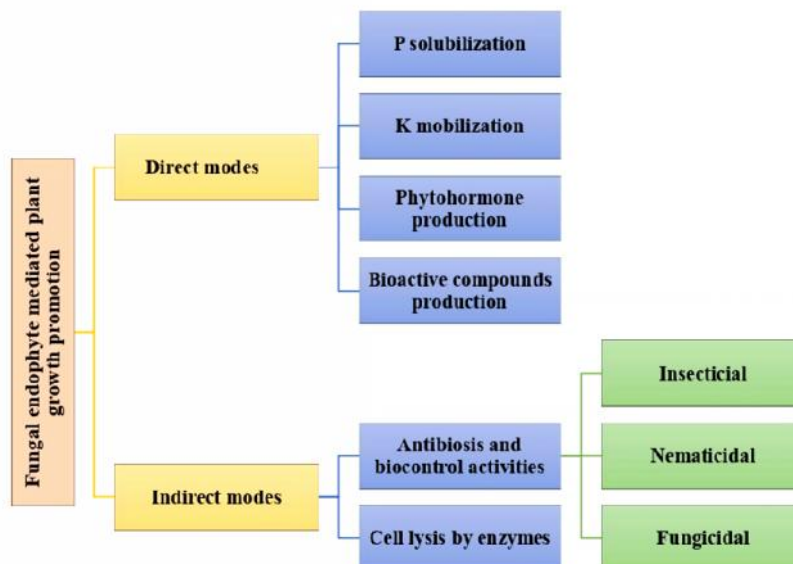


Fig. 3: Modes of fungal endophyte mediated plant growth promotion

However, their large-scale development suffers from bottlenecks of substrate specificity, low viability, transportation and storage loss. Newer potent FE-derived antifungal biomolecules can be industrially synthesized and marketed as a biopesticide. For example, the *Pinus taeda* endophytes, the strains of *Bacillus subtilis* and *Burkholderia* sp. were used as biological control agents against *Fusarium circinatum* (Soria et al., 2012). Also, the FEs control insect attacks by rendering the plant unpalatable to insects (Azevedo et al., 2000). Endophytes prevent herbivory by releasing bioactive compounds or by complex interacting elements of metabolic cycles. Defensive compounds can deter animal feeding and reduce pest occurrence in the field through ‘antixenosis’ and ‘antibiosis’ (Azevedo et al., 2000).

The FE *Neotyphodium* is an asexual, seed-borne fungal symbiont that mutualistically interacts with its grass hosts to provide several benefits, including increased growth, reproduction, and resistance to herbivores via endophytic alkaloids (Clay & Schardl, 2002; Faeth, 2009; Müller & Krauss, 2005). Such compounds belong to various chemical classes and include antibiotics, antioxidants, insecticides, antidiabetic agents and immunosuppressants. In particular, FEs produce amines and amide alkaloids (Glenn et al., 1996), indole alkaloids such as agroclavine, chanoclavine and elymoclavine (Powell & Petroski, 1993), pyrrolizidines (Bush et al., 1997), sesquiterpenes (Pulici et al., 1996), steroids (Lu et al., 2000), terpenoids (Souza

et al., 2011), diterpenes (Singh et al., 2000), isocoumarin derivatives (Koshino et al., 1992), quinones (Krohn et al., 2001), flavonoids (Ju et al., 1998), peptides (Strobel et al., 1999), phenols (Romeralo et al., 2015; Zou et al., 2000), phenylpropanoids and lignans (Koshino et al., 1988), aliphatic compounds (Koshino et al., 1989), chlorinated metabolites (Berek-Nagy et al., 2021) and volatile organic compounds (Morath et al., 2012). Such metabolites with non-hazardous and biodegradable properties could be pesticidal against the range of pests at relatively lower concentrations than chemical pesticides.

4. Conclusions

Endophyte research is open to some newer and exciting discoveries. However, several significant issues related to bioactive endophytes are still unresolved. Thorough research is required to tap the potential of FEs in agriculture. Also, better understanding and advanced strategies are needed to improve bioinoculant delivery, persistence and stability within the host. The FE point inoculation to plant is impractical for field applications. Alternatively, seed priming with FEs should be practiced for mass inoculations in crops. The use of FEs in biocontrol may remain limited until their ecology is well understood. As our understanding of FEs and their community will advance, the benefits of genetic manipulations will be significantly realized. The genetically manipulated FEs, which could disintegrate the pathogen cell wall and release pesticides can turn around the story of crop sustainability.

Plant traits and performance expression, including growth, nutritional status and environmental sustainability are due to the interaction between plant, microbiomes and the environment. In addition, the observed characters of the endophytes may change during plant inoculations due to complex endobiome interactions. For example, in the common palm tree, the intense light triggers pathogenicity of FE, *Iriarteia deltoidea*, while low light favors endophytism (Alvarez-Loayza et al., 2008). The study demonstrates the influence of abiotic factors on the distributions of endosymbionts in natural ecosystems. The ecology and molecular basis of host and endophyte interaction is yet to be understood. The factors responsible for endophyte colonization are also unknown. Also, the role of genetic and biomolecular factors accountable for host selection and colonization is yet to be explored.

The discovery of newer endogenous fungicidal metabolites is vital for the evolution of fungicidal molecules. It is believed that plants also synthesize bioactive metabolites, but the implication of endophytes in such biosynthesis is yet to be discovered. Preliminary studies support that endophytes facilitate bioactive metabolites to the plants. Several antifungal

metabolites have been isolated from a chemically diverse group of endophytic fungi found in terrestrial plants. The metabolites showed antifungal activity in laboratory experiments. These molecules can be confirmed as greener biocides when tested for toxicity to non-target organisms with no adverse effects on human health. In the near future, the effortful discovery of some new FEs followed by their genetic alterations for widespread host applicability could help find cost-effective and greener measures for achieving agricultural sustainability.

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DOI: 10.22192/enmpgp.2021	

How to cite this Chapter:

Anurag Yadav, Kusum Yadav and Rumana Ahmad. (2021). The Fungal Endophyte–Plant Interactions: Scope in Sustainable Agriculture. Sonali Priyadarshini, S. Panigrahi and C. C. Rath. (Eds), Endophytes: Novel Microorganisms for Plant Growth Promotion. India: Darshan Publishers. pp: 142-162.