

Applications of Fungal Endophytes in agriculture and medicine field

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Usage of beneficial microorganisms, commonly named as endophytes, is a novel approach to control the antibiotic resistance of pathogenic microorganisms both in agriculture and medicine. In addition, rising cost of production of chemical based drugs and environmental pollution caused by chemical fertilizers and pesticides is another fact to incline towards natural alternatives. Endophytic fungi are important source of novel compounds to be exploited in the sector of agriculture and medicine. The current paper explains the applications of endophytic fungi and the activity of various compounds produced by these microorganisms in the sectors of agriculture and medicine.

Keywords: *Endophytes, Biological control, Sustainable agriculture, Biodegradation*

Introduction

Endophytes can be defined as those organisms that colonize the internal tissues of the plant reside during certain time of their life span without harming it. They can be isolated from woody tree to herbaceous plant, monocotyledonous to dicotyledonous plant.(Miche and Balandreau 2001). Fungal endophytes are found to inhabit almost all of the tissues of the plant like root, stems, branches, leaves, flowers, fruit, seed and bark (Crozier et al. 2006). The endophytic microorganism is in mutualistic association with the host plant where endophytes obtain nutrients and minerals sufficient enough form host plant for their survival. On the

other hand, the endophytic microorganisms produce various bioactive chemicals in order to help host plant to defend the abiotic and biotic stress while benefiting the host for their growth. Among thousand different plant species, each of them is host to at least one endophytic microbial population. Even several thousand microbial strains are possible for a given endophytic species (Strobel *et al.* 2003). The endophytic growth depends upon manifold components such as: host species, host development, environmental factors and density of inoculum (Dudeja *et al.* 2014).

Endophytic fungi are widely exploited in the medicinal and agricultural field (Figure 1) to obtain the bioactive compounds present within them (Zhao *et al.*, 2011). The ability of bioactive compound to be used in wide range of fields has grabbed the attention for several years. Endophytic fungi are well known for their ability to produce various bioactive compounds possess multifarious bioactivities such as antimicrobial, insecticidal, cytotoxic, and anticancer activities. In some cases, the bioactive compounds produced by the fungi are also seen to be similar with those originated from their host plant. Because of the capability of these fungi to produce large number of plant growth-promoting chemicals, they are also recognized to ameliorate host plant growth and fertility of soil. Endophytic fungi could also be useful to the pharmaceutical industries by exploiting the active compound released by these microbes.

With rise of antibiotic resistance by pathogens, the necessity to search for new agents to antagonize the pathogenic microorganism by natural methods increased. The number of bioactive metabolites produced by endophytic fungi is found to be in greater number than other endophytic microorganisms. Moreover, about half of the of bioactive substances produced by the fungal endophytes were unknown earlier.. They are known to produce bioactive metabolites including steroids, terpenoids, diterpenes, isocumarins, quinones, lactones phenyl propanoids, lignans and aliphatic metabolites; extracellular enzymes

including cellulases, proteinase, esterases and lipases. Amines and amides, common endophytic metabolite, are seen to be toxic to insects without harming the mammals. A large number of plant are also reported to produce amines and amides which have the ability to solubilize phosphates present in insoluble form. They are also responsible for production of auxins, gibberellins, 1-aminocyclopropane-1- carboxylate (ACC) deaminase and cytokinins. Moreover, endophytic fungi have significant role to protect the host plant against the pathogens by promoting the host defense mechanism.

Role and Application of Fungal Endophytes

To escalate the plant production, 100 millions of tons of chemical fertilizer have been used annually. Most commonly used are potash, nitrogen and phosphate (Glick *et al.* 1999). The chemical fertilizers are associated with negative effects on the environment globally along with increasing the production cost of the food products. In order to enhance the growth and yield of plant, fungal endophytes can be used in sustainable agricultural practice; endophytes plays a role by consuming nutrients, consequently, conquering pathogens, and increase fitness of plant by conferring tolerance against stress (Vega *et al.* 2008). Secondary metabolites produced by endophytes help to minimize the damage by pathogen and promotes the defense of host against the pathogenic organisms by regulating the physiological response of plant (Gao *et al.* 2010).

Phytohormone production

Phytohormones are the chemicals that regulate the growth of plant. They are also having major roles in while plant faces biotic stress. Endophytes on other hand are also found to produce plant growth promoting hormones. There are various classes of phytohormones produced by the endophytes including Auxins, Gibberellins (GA), Indole Acetic Acid (IAA),

Abscisic acid (ABA), salicylic acid (SA), jasmonic acid (JA) and so on (Table 1) (Waqas *et al.* 2014).

Auxins, an important class of phytohormones, have a significant role in development and growth of the plant. Auxins is also found to play major roles in vascular differentiation, root and shoot orientation in response to gravity and light, division of cells, stem and root elongation, apical dominance and so on (Frankenberger *et al.* 1995; Patten *et al.* 1996; Aloni *et al.* 2006; Cecchetti *et al.* 2008). Auxins are also found to be involved onteraction between host and parasite(Hamill 1993; Gutierrez *et al.* 2009). Khan et al., 2015b isolated the two fungal strains, *Fusarium tricinctum* and *Alternaria alternate* from the leaves of *Solanumnigrum* and these strains were found to produce IAA and also promote the growth of Dongjin rice plants.

Endophytic fungi producing gibberellins increases growth of plants plant and promotes biomass under stressed conditions, and could be exploited to reduce the harmful effects of abiotic stresse (Khan *et al.* 2015). The aquatic plant *Trapa japonica*, containing endophytic fungi *Galactomyces geotrichum* produced biologically active GAs (GA1, GA4, and GA7) and IAA (Waqas *et al.* 2014). Moreover, two different fungi *Phoma glomerata* and *Penicillium* sp., isolated from the roots of cucumber, are studied to secrete IAA and gibberellic acid (GA3) as well as GA1, GA4 and GA7. The growth parameters, plant biomass and absorption of minerals (K, Ca and Mg) increased significantly while toxicity caused by sodium was alleviated, on inoculating the microorganisms in cucumber plants during stress conditions (Waqas *et al.* 2012). Khan et al., 2012 observed the similar effects with *Paecilomyces formosus* an another endophytic strain isolated from cucumber. Rim et al., 2005 studied the effect of *Fusarium proliferatum*, a fungal strainisolated from roots of *Physalis alkekengi* var. *francheti*, and reported apromotion in growth of plant even double than *F. fujikuroi*, a wild strain. This growth promotion was a result of production of the

physiologically active Gibberellic acid (GA1, GA3, GA4, and GA7, as well as GA9, GA20 and GA24) (Rim *et al.* 2005).

Moreover, endophytic fungus *Asprgillus fumigatus* TS1 and *Fusarium proliferatum* BRL1, isolated from roots of *Oxalis corniculata*, was found to increase the growth of *Wai-to-C*, a mutant rice. Promotion of growth was associated with the production of various types of GAs and IAA (Bilal *et al.* 2018). Similarly, endophytic basidiomycetous *Porostereum spadiceum* AGH786, capable of producing six different GAs, was found to promote the growth of soyabean and also was found decrease the effect of NaCl stress (Hamayun *et al.* 2017). Furthermore, the fungal endophytes *Penicillium citrinum* LWL4 and *Aspergillus terreus* LWL5, enhanced the growth of sunflower (*Helianthus annuus* L). These fungi were also found to reduce the stem rot caused by *Sclerotium rolfsii* in great extent; the content of salicylic acid and jasmonic acid was seen to increase in presence of disease (Waqas *et al.* 2015).

Similarly, other phytohormones produced by endophytic fungi play major on plant defense against stress stimuli. Salicylic acid (SA) jasmonic acid abscisic acid (ABA), are seen to respond against abiotic and biotic stress, and were found to play a role as defense signaling agent. Jasmonic acid stimulates the production of defensive proteins and secondary bioactive metabolites (Brodersen *et al.*, 2006; Balbi *et al.*, 2008). Salicylic Acid induces the systemic resistance against fungi promoting plant growth and thus playing a role in biotic and abiotic stress. Endophytic fungi producing GA and IAA, *Phoma glomerata* LWL2 and *Penicillium* sp. LWL3, are seen to promote the shoot length of rice significantly during drought and salinity. (Waqas *et al.*, 2012). An endophyte fungal strain *Galactomyces geotrichum*, isolated from *Trapa japonica*, inhabiting a Korean river is responsible for Induced Systemic Resistance (ISR) in soybeans and had a priming effect as indicated by production of significantly greater amounts of JA (Waqas *et al.*, 2014).

Similarly, endophytic fungus *Paecilomyces formosus* LWL was found to produce abscisic acid (ABA) and jasmonic acid (JA) in japonica rice under prolonged heat stress condition to protect the rice from heat (Waqas *et al.* 2015). The sunflower plants when inoculated with *Penicillium citrinum* and *Aspergillus terreus* was seen to alter SA and JA level of the plants, as compared to control plants which were infected or non-infected by pathogen *Sclerotium rolfsii* (Waqas *et al.* 2017). Moreover, extracellular enzymes like cellulose, pectinase, xylanase, amylase and gelatinase were produced by three different endophytic fungus; *Alternaria alternate*, *Penicillium chrysogenum* and sterile hyphae, isolated from medicinal plant *Asclepias sinaica*. These endophytic fungal strain produced Indole Acetic Acid (IAA) and ammonia resulting in growth of root (Fouda *et al.* 2015). Endophytic fungi *Penicillium sp.*, *Chrysosporium pseudomerdatium*, *Paecilomyces sp.*, *Phoma glomerata*, *Aspergillus fumigates* and *Paecilomyces formosus* produced gibberallic acid and indole-3-acetic acid and also promoted chlorophyll contents, shoot length, and biomass of both wild and mutant- type rice (Waqas *et al.*, 2014).

Biocontrol Agents

Farmers are using various measures to controlling pest, disease causing pathogen or any other invasive species in plants. One way to control those foreign agents is by the use of living organism or its metabolites. This is known as biological control or biocontrol. It is the natural method of controlling foreign bodies on the host plant by reducing the dependency of chemical pesticides as synthetic chemical pesticide and herbicide uses have shown to impart negative health consequences on the public health (USNRC 1993). The role of endophytic fungi in agricultural sector as biocontrol agent is one of the most studied fields of endophytes (Table 2). Endophytic fungi are widely used as insect repellent, insecticidal agent, plant

growth promoters and plant pathogen inhibitors (Selim *et al.* 2017). Endophytic fungi are reported to modify of plant disease. This modification may be from pathogen antagonism to pathogen facilitation; depending upon the type and group of endophyte and nature and type of pathogen found in the host plant. Pathogen antagonism is the most common measure found among the host plant (Busby *et al.* 2016). Various studies have reported the mitigation of pathogenic diseases after the inoculation of common endophytic fungus in the plants. Some of those endophytic fungi are *Fusariumverticillioides*, *Acremoniumzeae* (Poling *et al.* 2008).

Similarly, widely used medicinal plant, *Rawwolfia serpentine*, found of Assam is seen to host endophytic fungi *Nigrospora*, *Trichoderma* and *Curvularia* having antagonistic properties against *Phytophthora* spp. and *Fusarium oxysporum* (Doley and Jha 2010). Similarly, endophytic fungi *Aspergillus niger* and *A. flavus* isolated from *Cannabis sativa* is seen antagonist to plant pathogenic microorganisms, *Colletotrichum gloeosporioides* and *Curvularia lunata* (Gautam *et al.* 2013). Moreover, endophytic fungi are also found to inhibit and reduce the condition of various plant diseases. Witches Broom Disease in Cacao is caused by the basidiomycete fungus *Crinipellis pernicioso*. Endophytic fungi *Gliocladium catenulatum* was found to inhibit the pathological condition in cacao seedling by 70% (Rubini *et al.* 2005). An endophytic fungus *Phaeosphaeria nodorum*, isolated form leaves of plum (*Prunus domestica*), was reported to produce inhibitory volatiles preventing the growth of fungus *Monilinia fructicola*; causes blossom blight, brown rot and twig blight of stone fruits (Pimenta *et al.* 2012). Furthermore, endophytic fungal strain from cotton roots, CEF-818 (*Penicillium simplicissimum*), CEF-642 (*Talaromyces flavus.*), CEF-714 (*Leptosphaeria sp.*) and CEF-193 (*Acremonium sp.*), were used to assess their effects against *V. dahliae* strain Vd080 which causes verticillium wilt in cotton. Results indicated that these endophytes both delay as well as reduced the symptoms of cotton wilt(Yuan *et al.* 2017). *Endophytic*

fungus Cryptosporiopsis quercina, isolated from medicinal plant *Tripterigeum wilfordii* demonstrated antifungal properties against *Candida albican* (Strobel *et al.* 1999). Bioactive compounds Cryptocandin and Cryptocin, isolated from *Cryptosporiopsis quercina*, were found to be responsible for antifungal activity. Cryptocin acts as an antifungal agent against several pathogenic plant fungi.

Strategic management when involved in agricultural practices helps to reduce the dependence on excessive use of fungicides to maintain ecofriendly sustainable farming practice. Two endophytic fungi *Penicillium citrinum* and *Aspergillus terreus* are seen to enhance the growth of sunflower plant and reduce the adverse effect caused by stem rot (Waqas *et al.*, 2017). The growth of plant was increased during the diseased condition by inoculating fungal endophytes on host plant by regulating host plant defense responses. Moreover, studies show that endophytic fungi are also involved in control of nematode. They help to develop defense against the harmful nematodes in plants. Such endophytes help to improve sustainability in agricultural practices even though the actual mechanism is poorly understood (Schouten *et al.* 2016).

Furthermore, endophytic fungi are also associated in controlling insecticides. Endophytic fungus *Phomopsis oblonga* was the first endophyte reported to act against *Physocnemus brevilineum*, beetle present on elm tree (Webber, 1981). Ergot alkaloids and mycotoxins produced by endophytic fungus *P. oblonga* was found to reduce the spread of *Ceratocystis ulmi*, responsible for spreading Dutch elm disease, by regulating its vector *P. brevilineum*. Endophytic fungus *Bontia daphnoides*, which produced metabolites nodulisporic acids and novel indole diterpenes, was having potential insecticidal properties against bowl fly larva (Demain 2000). Endophytic fungus *Muscodor vitigenus*, producing an active ingredient naphthalene, isolated from liana plant (*Paullina paullinioides*) is used against the control of mothballs (Daisy *et al.* 2002). Endophytic fungal isolates from strawberry leaves

belonging to *Paecilomyces* genera were responsible to induce death of *Duponchelia fovealis*, a pest found in strawberries (Amatuzzi *et al.* 2017). Similarly, the borer insets in coffee seedlings were found to be controlled by *Beauveria bassiana*, also known as entomopathogen (Posada *et al.* 2006).

Phytostimulation and Plant Growth Promotion

The growth promotion of plants by microorganisms occurs by direct or indirect pathway (Glick, 1995). Endophytic fungal strains are seen to promote plant growth by producing growth promoting agents.

Phosphorus (P) is responsible for stimulating growth and promoting maturity of plant. As it is an essential nutrient for plant, deficiency leads to stunted growth, delay in maturity, and reduction in yield (Mallarino *et al.* 2002; Loria and Sawyer, 2005). Two isolates of *Penicillium* sp., isolated from *Camellia sinensis*, showed the solubilization of tri-calcium phosphate (Nath *et al.* 2012a). Similarly, endophytic fungi *Trichoderma pseudokoningii* found in tomato roots in central Himalayan region, resulted in and auxins, HCN, ammonia and siderophores production as well as solubilization of phosphate. All this is activities are associated with plant growth promotion (Chadha *et al.* 2015).

Similarly, iron acts as a cofactor of various enzymes and is an essential nutrient for overall plant metabolism. Mostly iron is present in ferric hydroxide form in the soil limiting the utilization and growth of plant even with the presence of iron in soil. Siderophores are produced by microorganisms in iron deprived conditions. It helps in binding Fe^{3+} and uptake of iron into the plant tissues (Glick *et al.* 1999). Various endohytic microorganisms are seen to produce siderophores. Ferricrocin siderophore is associated to be released by endophytic fungi present in *Pinus sylvestris* L (Scots pine) and *Rhododendron tomentosum* Harmaja (Labrador tea) (Kajula *et al.* 2010). Moreover, *Camellia sinensis* plant grown in Assam, India is found to host for *Penicillium sclerotiorum*, *Aspergillus niger*, *P. chrysogenum* and

Fusarium oxysporum. These endophytes are also found to be responsible in production of auxin; solubilization of phosphate, potassium and zinc (Nath *et al.* 2012b). Likewise, endophytic fungi *Penicillium citrinum* and *Aspergillus terreus* promoted the growth of sunflower (*Helianthus annuus* L.) and enhanced resistance against the stem rot disease caused by pathogen *Sclerotium rolfsii* (Waqas *et al.*, 2015).

Biodegradation and bioremediation

Biodegradation is a process of transformation of utilized nutrients by the use of bacteria, fungi or any other biological means back to ecosystem. Endophytic fungi are responsible for biodegradation of the litter produced by the host plant (Promputtha *et al.* 2010). Endophytic fungi responsible for decomposing cellulose, hemicellulose, lignin and other organic components have different ability (He *et al.* 2012).

Chitin forms the exoskeleton of insects as well as the structural component of fungal cell wall. Enzyme chitinases degrades the insoluble polymer of chitin. The carbon and nitrogen present within chitin are degraded by endophytic fungi and thus contributes the ecosystem (Kellner and Vandenbol, 2010). Chitinase enzyme and its isoform was found to be produced by endophytic fungi isolated from tree leaves of Western Ghats, India forest (Rajulu *et al.* 2011). Bioremediation is a technique of removal of waste materials with the use of microorganism from the environment. According to reported literatures, endophytic fungi as well as bacteria are shown to have strong potential of breaking complex molecules.

The decline in growth, yield and quality of crop is associated with cinnamic acid found in cropping soils. The degradation of cinnamic acid to styrene was carried out by endophytic fungus *Phomopsis liquidambari*. Enzymes such as laccase, hydroxylase and phenolic acid decarboxylase were involved during this process (Xie and Dai 2015). Endophytic fungi were found to have the properties of degrading the petroleum contaminants present in the soil

leading to promotion of growth of host plant (Krishnamurthy *et al.* 2017). Some of the serine hydrolase producing endophytic fungi were found to degrade the polyurethane, a plastic material found in various forms (Russel *et al.* 2011). The phytoremediation of hydrocarbon concentrated soil is also performed by endophytic fungi. Endophytic fungi *Lewia* sp. helped in phytoremediation of hydrocarbon contaminated from both perlite and soil of *Festuca aruninaceae* (Krishnamurthy *et al.* 2017). Endophytic fungi are also helpful in degrading polyaromatic hydrocarbons (PAHs). The degradation of phenanthrene was reported by *Ceratobasidium stevensii* isolated from plant *Euphorbiaceae* (Dai *et al.* 2010) and by *Phomopsis* isolated from rice plant (Tian *et al.* 2007).

Fungal Endophytes as Source of Bioactive Compounds

The discovery of bioactive compounds from the microorganism has skyrocketed in last 50 years. More than 30,000 natural products have been discovered only after 1940 from microorganism among which over 10,000 were found to be biologically active (Fenical *et al.* 2006). The metabolic bio-products of endophytic microorganisms are found to be extremely useful for both the plant and animal. These novel compounds are used by the plants against foreign pathogen and these compounds are also used for the discovery of new drugs. Studies shows hundreds of bioactive natural products like steroids, alkaloids, terpenoids and flavonoids are produced by the endophytic microorganisms with various properties such as antioxidants, antibiotics, anticancer and immune-suppressants (Figure 2).

Anticancer

Endophytes are good candidates in drug discovery due to their property to produce novel compounds with antibiotic, antiviral and anticancer properties. Taxol, a diterpenoid compound, was initially isolated from *Taxus brevifolia* (Stierle *et al.* 1993). This compound

later turned out to be the world's first billion dollar drug against cancer and most importantly facilitated the further research on endophytic microbes of plant for its potential use in medical field. Few years after, endophytic fungus *Taxomyces andreanae* isolated from inner bark of *Taxus brevifolia* plant was found to produce taxol. (Selim *et al.* 2012). Another endophytic fungi *Pestalotiopsis microspore* found in *Taxus wallichiana* and plants were also found to produce taxol (Strobel *et al.* 1996).

Gangadevi and Muthumary 2008 and Liu *et al.* 2009 isolated an endophytic fungus *Colletotrichum gloeosporioides* from the leaves of *Justicia gendarussa* was found to produce taxol, commonly used to cure breast cancer, ovarian cancer and lung cancer. Taxol also produced by *Lasiodiplodia theobromae*, endophytic fungus, isolated from *Morinda citrifolia* is reported to have cytotoxic activity breast cancer cell line of human (Pandi *et al.* 2011). Some other anticancer compounds produced by endophytic fungus are camptothecin, vincristine and podophyllotoxin (Redman *et al.* 2001). Similarly, many anticancer compounds are isolated from fungal species having different chemical activity against different cell lines. The extract of *Cordyceps militaris* was found to inhibit the growth of MCF-7 human breast cancer cells by response of dose upon time (Xu 2008). Fungal extract was able to reduce DNA methylation by suppressing methyltransferase transcripts and hence recovering tumor suppressing genes and inhibiting growth of tumor. Endophytic fungus isolated from *Juniperus communis* L. Horstmann has been reported to produce deoxy-podophyllotoxin (Kusari *et al.* 2009). Similarly, novel bioactive metabolites were isolated from endophytic fungus *Alternaria alternata* residing in *Maytenus hookeri* and were characterized by NMR as alternariol, (ii) alternariol monomethyl ether, (iii) 5-epialtenuene, (iv) altenuene, (v) uridine, (vi) adenosine, ACTG toxin-E, (viii) ergosta-4,6,8,22-tetraen-3-one.

In a study carried out by Banu and Kumar (2009), antimicrobial and antitumor activities were shown by endophytic fungus isolated from medicinal plant in yeast cell based assay.

Moreover, antimicrobial screening of isopropanol extract obtained from endophytic fungi against *Bacillus subtilis*, *Saccharomyces cerevisiae* and *Alternaria* sp. was performed in India. Similarly, a marine endophytic fungus *Aspergillus terreus* has been shown to produce compounds with anticancer activity (Suja *et al.* 2014). Another species of *Aspergillus*, *Aspergillus tubingensis*, showed inhibitory response against tumour cell lines of MCF-7, MDA-MB-435, Hep3B, Huh7, SNB19 and U87 MG; monomeric naphtho-g-pyrogens TMC 256 A1 was responsible for antitumour activity (Huang *et al.* 2011b). Similarly, endophytic fungi *Rhinoctadiella* sp. present in *Tripterygium wilfordii*. produced novel cytochalasins which possess cellular toxicity resulting in antitumor activity (Wagenaar *et al.* 2000).

The endophyte having genus *Pestalotiopsis* shows higher number of antitumour activity. *Pestalotiopsis microspora*, was reported to produce Torreynic acid having anticancer properties. Torreynic acid was found to be cytotoxic in nature and capable of cell apoptosis (Li *et al.* 1996). *Pestalotiopsis microspore* found in inner bark of *Taxus sp.*, is also seen to produce taxol (Strobel *et al.* 1996). Another strain of *Pestalotiopsi* has been identified to have maximum concentration of taxol. *Pestalotiopsi versicolor* produced 9560 times more taxol than *Taxomces andreanae* in culture broth (Kumaran *et al.* 2010).

Antimalarial Activity

Parasitic infections like malaria are one of the major concerns for developing nations. Every year two to three millions people are dying because of malarial infections. Natural products widely used to discover drugs against several diseases including malaria. Chloroquine and quinine are the most commonly used antimalarial drugs but are having reduced effectiveness as a result of resistance. Hence search for new anti-parasitic drugs is still equally important. Endophytic fungi, *Xylaria sp.*, were found to produce two novel metabolites of benzoquinone along with other two known compounds. In vitro analysis showed that these compounds were antagonistic in nature to K1 strain of *Plasmodium*

falciparum, one of the causative agents of malaria (Tansuwan *et al.* 2007). Similarly, three different novel dihydroisocoumarin derivatives isolated from endophytic fungus *Geotrichum sp.* present in *Crassocephalum crepidioides* were found to be having antimalarial with anti-tuberculosis and antifungal properties (Kongsaree *et al.* 2003). The extracts of endophytic fungi were isolated from *Psidium guajava*, *Azadirachta indica*, *Newbouldia laevis* and *Agerantum conyzoides* from Nigeria. In vitro antiplasmodial test against *Plasmodium berghei* showed positive result indicating the presence of antiplasmodial along with immunomodulatory activities (Nonye *et al.* 2017). Fifty one endophytic fungi were isolated from *Garcinia* species and sixty-five crude extracts were isolated from those endophytes. The bioactivities of fungal extracts showed that 14.1% were having antimalarial activities (Phongpaichit *et al.* 2007).

Antimicrobial Activity.

Endophytes isolated from medicinal plants are widely known for their several antimicrobial activities (**Table 3**). They are seen to control and inhibit the pathogens in plants and animals. The bioactive compounds isolated from endophytes have wide spectrum of activity against pathogenic microbes. The bioactive assay of endophytic microbes like *Thielavia subthermophila*, *Dothideomycetes sp.*, *Alternaria tenuissima*, *Alternaria sp.*, *Colletotrichum truncatum*, *Nigrospora oryzae*, and *Chaetomium sp.*, isolated from the medicinal plant, *Tylophora indica*, were found to inhibit the growth of *Sclerotinia sclerotiorum* and *Fusarium oxysporum* (Kumar *et al.* 2011). Similarly several other endophytic fungi like *Guignardia sp.*, *Botryosphaeria sp.*, *Fusicoccum sp.*, *Muscodora sp.*, *Aspergillus sp.*, *Penicillium sp.*, *Pestalotiopsis sp.*, *Curvularia sp.* and *Phomopsis sp.* showed antibacterial, antimalarial, antiviral, and antioxidant activity (Phongpaichit *et al.* 2007). Cryptocandin produced by endophytic fungus *Cryptosporiopsis cf. quercina*, isolated from hard wood of *Tripterigeum wilfordi*, was seen to have antifungal actions against *Candida*

albicans, responsible for causing candidiasis in human (Strobel *et al.* 1999). Similarly, pestaloside, a bioactive compound isolated from endophytic fungus *P. microspore* present in *Torreya taxifoli* (Julie *et al.* 1995) and CR377 isolated from *Fusarium* sp. present in *Selaginellapallescens* were found to have antifungal properties (Sean *et al.* 2000). Jestoerone is an antifungal compound isolated from endophytic fungi *Pestalotiopsis jester* (Li *et al.* 2001).

Moreover, *Colletotrichum gloeosporioides*, an endophyte isolated from *Artemisia mongolica*, was reported to synthesize a bioactive compound Colletotric acid having antibacterial actions (Zou *et al.* 2000). Novel compound javanicin was synthesized by endophytic fungus *Chloridium* sp, isolated from *Neem* plant, showing antibacterial properties against *Pseudomonas* sp (Kharwar *et al.* 2009). Similarly, endophytic fungus *Cytonaema* sp. responsible for producing Cytonic acid A and B is seen to inhibit human cytomegalovirus (hCMV) protease (Guo *et al.* 2000). Diaportheone A and B are two benzopyranones extracted from the endophytic fungus *Diaporthe* sp. present in *Pandanus maryllifolius* leaves. Both, diaportheone A and B were seen to inhibit the growth of *Mycobacterium tuberculosis*H37Rv (M. E. Bungihan *et al.* 2011).

Antioxidants

Reactive oxygen species and free radicals cause oxidation of biomolecules of human body resulting in inflammation, coronary heart diseases, atherosclerosis, tumors, ageing, and neurodegenerative diseases and so on. Antioxidants are responsible in scavenging free radicals and reactive oxygen species; thus helping to reduce the risk of many diseases. The bioactive natural compounds produced by the endophytic fungi having antimicrobial, anticancer, insecticidal, pesticidal and antagonistic characteristics are also found to be antioxidant in nature (Strobel *et al.* 2004). A study on 292 morphologically different endophytic fungi isolated from several medicinal plants indicated the strong antioxidant

activities by several fungal metabolites (Huang *et al.* 2007). Isopestacin, obtained from endophytic fungus *Pestalotiopsis microspore*, possessed antifungal as well as antioxidant properties. Isopestacin was found to inhibit superoxide and hydroxyl free radicals as when measured by electron spin resonance spectroscopy (Strobel *et al.* 2002). Aryl tetralin ligans, produce by endophytic fungus *Trametes hirsute* and used in synthesis of topoisomerase inhibitoes, was biologically active and had antioxidant properties along with anticancer properties (Puri *et al.* 2006).

Similarly, antioxidant properties of endophytic fungal extracts are also screened in-vitro condition. An endophytic fungus *Phomopsis* sp. GJJM07, isolated from medicinal plant *Mesua ferrea*, was found to have potential antioxidant activity when evaluated for free radical scavenging (DPPH) activity (Jayanthi *et al.* 2011). Moreover ,the endophytic fungal extracts of *Chaetomium* sp., *Aspergillus* sp., *Aspergillus peyronelii* and *Aspergillus niger* strainisolated from *Eugenia jambolana*, when screened for in vitro antioxidant activity showed antioxidant activity in the range of 50% to 80% (Yadav *et al.* 2014). *In-vitro antioxidant activity of endophytic fungus Aspergillus fumigates isolated from pigeon pea showed the presence of luteolin, an antioxidant compound, in EtOAc fraction of MD-R-1, major compound of endophytic fungi. Luteolin is also used in food industry as natural antioxidant (Zhao et al. 2014).*

Conclusion

In recent years, many researchers had done bioprospecting of endophytic microbes, great work has been done regarding endophytic activity of three different classes of microbes-actinomycetes, fungi and bacteria. All these endophytic microbes playing great role in agriculture and medicinal fields. They are producing various bioactive novel compounds so they are highly beneficial for crops and mankind. As they also have the growth promoting role

to enhance the crop productivity by releasing various hormones, bacteria play major role regarding this. Fungi has the role in antibiotics, bioremediation etc. Actinomycetes also have growth promoting activity. So overall we can conclude these are highly advantageous as do not cause any harmful effect so can be utilized in many prospects. So much more novel compounds must be exploited from these microbes, keeping in view future aspects as most of pathogens becoming resistant to medicines, fertilizers etc.

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Table 1: Phytohormones produced by endophytic fungi

Endophyte	Host plant	Phytohormones	References
<i>Fusarium tricinctum</i> and <i>Alternaria alternata</i>	<i>Solanum nigrum</i>	IAA	Khan et al. 2015b
<i>Galactomyces geotrichum</i>	<i>Trapa japonica</i>	GAs (GA1, GA4, and GA7) and IAA	Waqas et al. 2014.
<i>Fusarium proliferatum</i>	<i>Physalis alkekengi</i>	GA1, GA3, GA4, and GA7, as well as GA9, GA20 and GA24	Rim et al. 2005
<i>Aspergillus fumigatus</i> TS1 and <i>Fusarium proliferatum</i> BRL1	<i>Oxalis corniculata</i>	GAs and IAA	Bilal et al. 2018
<i>Penicillium citrinum</i> LWL4 and <i>Aspergillus terreus</i> LWL5	-	Salicylic acid and jasmonic acid	Waqas et al. 2015
<i>Alternaria alternata</i> , <i>Penicillium</i>	<i>Asclepias</i>	IAA	Fouda et al.

<i>chrysogenum</i>	<i>sinaica</i>		2015
Endophyte	Host plant	Action	References

Table 2: Endophytic fungi as biocontrol agent

<i>Penicillium copticola</i>	<i>Cannabis sativa</i>	Inhibition of growth of <i>Botrytis cinerea</i> and <i>Trichothecium roseum</i>	Kusari et al. 2013
<i>Penicillium simplicissimum</i> , <i>Leptosphaeria</i> sp., <i>Talaromyces flavus</i> . and <i>Acremonium</i> sp.	Cotton	Incidence and index of verticillium wilt was lowered	Yuan et al. 2017
<i>Gliocladium catenulatum</i>	Cacao plant (<i>Theobroma cacao</i> L.)	Inhibition of pathological severity by <i>Moniliophthora perniciosa</i>	Rubini et al. 2005
<i>Phaeosphaeria nodorum</i>	Plum (<i>Prunus domestica</i>)	Inhibition of growth and reduction in width of <i>Monilinia fructicola</i>	Pimenta et al. 2012
<i>Nigrospora</i> , <i>Trichoderma</i> and	<i>Rawwolfia serpentine</i>	Antagonism against <i>Phytophthoa spp.</i> and <i>Fusarium</i>	Li et al. 2000, Doley and Jha 2010
<i>Phomopsis oblonga</i>	Elm Tree	Antagonism against <i>Physocnemum brevilineum</i>	Webber 1981
<i>Penicillium citrinum</i> and <i>Aspergillus terreus</i>	-	enhance the growth of sunflower plant and reduce the adverse effect caused by stem rot	Waqas et al. 2017).
<i>Aspergillus niger</i> and <i>A. flavus</i>	<i>Cannabis sativa</i>	Inhibit plant pathogenic microorganisms, <i>Colletotrichum gloeosporioides</i> and <i>Curvularia lunata</i>	Gautam et al. 2013

Table 3: Endophytic fungi as antimicrobial agent

Endophyte	Host plant	Bioactive compound	Action	References
<i>Cryptosporiopsis</i> cf. <i>quercina</i>	<i>Tripterigeum wilfordi</i>	Cryptocandin	Antifungal actions against <i>Candida albicans</i>	Strobel et al. 1999
<i>P. microspore</i>	<i>Torreya taxifoli</i>	Pestaloside	Antifungal properties	Julie et al. 1995
<i>Pestalotiopsis jester</i>	-	Jestoerone	Antifungal properties	Li et al. 2001
<i>Colletotrichum gloeosporioides</i>	<i>Artemisia mongolica,</i>	Colletotric acid	Antibacterial properties	Zou et al. 2000
<i>Chloridium</i> sp.	Neem plant	Javanicin	Antibacterial properties	Kharwar et al. 2009
<i>Cytonaema</i> sp	-	Cytonic acid A and B	Inhibition of human cytomegalovirus (hCMV) protease	Guo et al. 2000
<i>Diaporthe</i> sp.	<i>Pandanus maryllifolius</i>	Diaportheone A and B	Inhibition of the growth of <i>Mycobacterium tuberculosis</i> H37Rv	Bungihan M E et al. 2011).

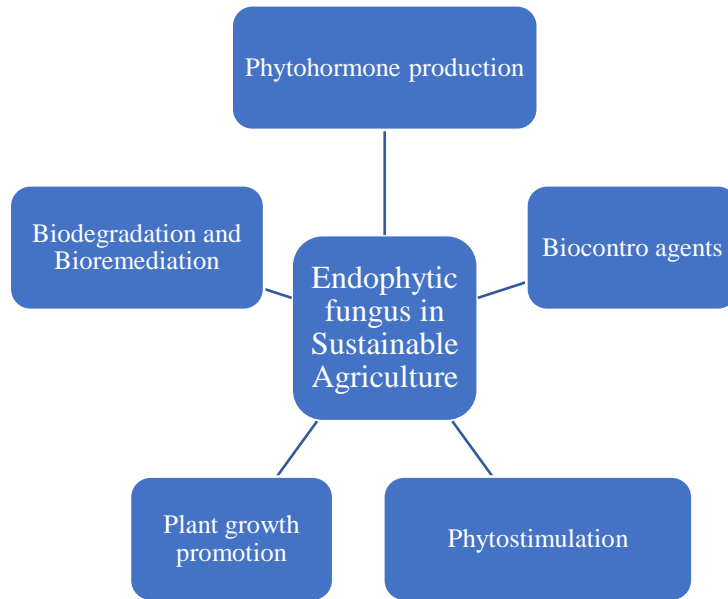


Figure 1 : Role of endophytic fungus in sustainable agricultural practices

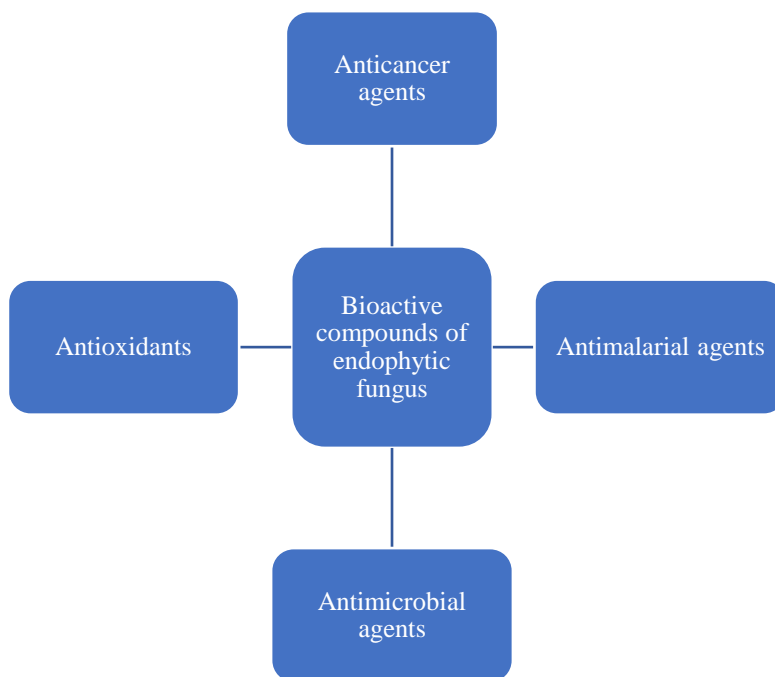


Figure 2 : Role of bioactive compounds form endophytic fungus

