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RESEARCH ARTICLE

A SHORT REVIEW – ENDOPHYTIC FUNGI IN MEDICINAL PLANTS

*Manisha R. Survase and Santosh D. Taware

Mahatma Gandhi Mission, Institute of Biosciences and Technology, Aurangabad-431003, India

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ABSTRACT

Medicinal plants are known to be used for centuries which are still being used for their health benefits and are a valuable source for bioprospecting endophytes. These days medicinal plants are exploited for the isolation of plant-derived drugs as they are effective and have relatively less or no side effect, due to which medicinal plants are getting exhausted. Endophytes are ubiquitous organisms found in plant bodies that constitute an important component of microbial diversity. Endophytic fungi reside in the host plant without causing apparent symptoms of infection. Endophytes are gaining attention as a subject for research, medicinal, agricultural potential and application in plant pathology due to their benefits for the host plant in defense and development. The review reveals the importance of endophytic fungi from medicinal plants as a source of bioactive and chemically novel compounds.

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INTRODUCTION

Overexploitation of forest resources has led to enormous loss of species. Due to this exploitation of forest resources most existing medicinal plant species in India have become endangered as they are used as raw material for herbal industries thus creating a threat to natural populations of medicinal plants (Zabalgogeazcoa, 2008). Endophytes are an important component of microbial niche affecting the plant in various forms. The term "endophyte" was first derived by De Barry (1866) (Sun and Guo, 2012). Many endophytic fungal species inhabit the tissues of the plant body (Zabalgogeazcoa, 2008). These endophytic fungi have been widely studied in various geographical and climatic zones and have been found to be associated with plants for over 400 million years (Krings et al., 2007). Since individual plants can harbor dozens of endophytic fungal species, assemblages of these endophytes are hence influenced by their geographic location, age, the specificity of tissue colonization (Bhagat et al., 2012). Endophytic fungi belong to a poly-phyletic group, mostly belonging to ascomycetes and anamorphic fungi. Endophytes are presumably ubiquitous in plants that reside in healthy tissues and organs such as roots, stem, leaves, branches and exhibit complex interaction with the host body. According to the study, the endophytic fungal species were found to have a mutualistic, parasitic and antagonistic relationship with the host plant (Rodriguez et al., 2009). Some endophytes are found to be co-evolved with their host plants and have developed the ability to produce identical bioactive substances as their host plants. They are known to affect the interaction of plants with their environment to alter their interaction with plant pathogens (Zabalgogeazcoa, 2008). Endophytic fungi play a particular role in their host such as defense from a pathogenic microorganism, growth of plant body, solubilization of essential nutrients for host plants. The plant provides nutrients to the fungi, while the fungi produce factors that protect the plant from the attack by insects, animals or microbes and also, it helps plants against herbivory from grazing animals (Raviraja, 2005). It is found that endophytes are mutualistic in nature, conferring tolerance to biotic and abiotic stress conditions in the host thus enhancing growth and survival of plants in adverse conditions (Shubin et al., 2014). Based on their nature, endophytes are categorized into three groups:

- Pathogens of another host that are non-pathogenic in their endophytic relationship,
- Non-pathogenic microbes,
- Pathogens that have been rendered non-pathogenic but are still capable of colonization by selection method or genetic alteration (Gond et al., 2012).

The accepted estimate of 1.5 million fungi on earth is primarily based on the ratio of vascular plants to fungal species of 1:6,

***Corresponding author:* Manisha R. Survase,**
Mahatma Gandhi Mission, Institute of Biosciences and Technology, Aurangabad-431003, India.

but endophytic fungi have not been considered in the estimation (Hawksworth, 1991). Furthermore, Petrini suggested that there could be more than 1 million species of endophytic fungi still remaining to be discovered and described based on ratios of vascular plants to fungal species of 1:4 or 1:5 (Petrini, 1991). Endophytic fungi play an important role in enhancing plant health and have been recognized as an important resource of biocontrol agents to suppress plant pests including insects and pathogens (Xiang et al., 2016). Medicinal plants, however, have been recognized as a repository of fungal endophyte with novel metabolites of medicinal and pharmaceutical importance. It has been mentioned that compounds isolated from medicinal plants may not be plant metabolites but maybe from fungal metabolites (Patil et al., 2015). Development in screening technologies portrays that endophytic microorganisms are an untapped source of diverse metabolites, therefore microflora of medicinal plants is considered as a new domain to be explored. Since medicinal plants are thought to provide a unique environment for endophytes for the production of novel metabolites, they are considered to have great potential in medicinal and agricultural applications (Sun et al., 2014). As the contribution of endophytes in medicinal plants is unknown it has thus created a platform for investigators to discover novel genes and compounds.

As per the study, plant pests and pathogens including viruses, nematodes, insects, fungi reduce plant yield by 30-50 % globally (Mousa and Raizada, 2013). Thus, the host –fungal symbiosis may be beneficial to host conferring resistance to insects, pests, and herbivores(White et al., 1987). Different biosynthetic pathways synthesize different bioactive compounds belonging to different structural groups such as terpenoids, phenols, quinones, steroids, coumarins, etc.(Kaul et al., 2012), exploration of these endophytes for such bioactive compounds may add to the applied and ecological perspective of the endophytic community.

What are endophytes: Endophyte refers to an organism that lives within a plant body, where “endo” means “inside” and “phyte” means “plants”(Wilson, 1995). Endophytes may include bacteria, fungi, and actinomycetes(Bhagat et al., 2012) that live in intercellular space called “apoplast” of the host plant as well as inside the cell called “symplast” (Saikkonen et al., 1998). Endophytic fungi mainly consist of members of Ascomycota as well as some taxa of Basidiomycota, Zygomycota, Oomycota (Rajamanikyam et al., 2017). These endophytes reside into the host body for all or part of their life cycle without causing any obvious symptoms or any negative effect (Bhagat et al., 2012; Zabalgogeazcoa, 2008), but can act as pathogen to a plant species other than its host (Schulz et al., 1998). Most of the vascular plants are found to harbor endophytic microorganisms (Rodriguez et al., 2009).

Any single plant organ such as leaf, stem or root of a plant can harbor many different species of endophytes. It has been found that some endophytic bacteria may live within endophytic fungi (Hoffman et al., 2013). Some of the studies suggest that few endophytes help in nitrogen fixation while, some endophytes are thought to have enhanced host growth, nutrient acquisition and improve plant to tolerate abiotic stresses (Gibert et al., 2015), such as drought (Khan et al., 2015) and decrease biotic stresses by enhancing plant resistance to insect, pathogens, and herbivores (Raviraja, 2005). The most commonly associated organisms are fungi and bacteria although there are some endophytic algae (Gimenez et al., 2007) and oomycetes (Derevnina et al., 2016). Due to extensive studies of such groups of endophytes, they were further divided into different subgroups, such as, “obligate” or “facultative” which are associated with all types of plants (Rosenblueth and Martínez-Romero, 2006). The endophytes that depend on the plant for their survival, which is being spread by any vector or by vertical transmission are termed obligate endophytes (Hardoim et al., 2008). Whereas, the endophytes which stay outside the host body for certain period of the life cycle and are associated with plants from its neighboring soil environment and atmosphere are termed as facultative endophytes.Endophytes harboring plants produces secondary metabolites and synthesizes other chemicals which make the plant more resistant to the nematode, insects, and livestock and also enables the plant to grow faster due to production of phytohormones which make them become competitive that they dominate in particular environment (Kaul et al., 2012).

Redman et al. (1999) mentioned that endophytes may be a single-gene mutant of a wild pathogenic type which makes it unclear whether plant isolated fungi are actually endophytes or are latent pathogens. For example, *Diaphorte phaseolorum* is a known pathogen causing pod and stem blight in legumes, but also can live as an endophyte and produces spores once the host plant is dead (Schwarz et al., 2004). Endophytes may produce abundant bioactive metabolites that may be involved in host endophyte relations and may serve as a potential source of novel natural products for exploitation in various fields such as medicine, agriculture, industry, etc. (Bacon and White, 2000).

Transmission of Endophytes in the host plant: Endophytes may be transmitted either vertically or horizontally (Saikkonen et al., 2015). Vertical transmission takes place when the seed gets infected by the fungal endophyte and then transmitted to the plant which is typically considered clonal and transmit via fungal hyphae penetrating the embryo within the host’s seeds (e.g., seed transmitting forms of *Epichloë* (White et al., 1993b).This transmission is considered to be a kind of systemic infection that allows an endophyte to get into the seed during its formation period, such as *Neotyphodium* species which results in an infected population (Scott, 2001). Horizontal transmission requires the production of asexual or sexual spores, where endophyte may spread between the plant in a population or community (Tadych et al., 2014). This preferred mechanism is for those associated with woody species and localized in certain organs of the host plant (K. Saikkonen et al., 1998). The spores can be sexual (ascospores) or asexual (conidia) which can be transmitted by insects leading to spore dispersion (Gimenez et al., 2007). Some endophytes that are transmitted vertically may produce spores on the plant that get transmitted horizontally (e.g., *Epichloë festucae*) (Chung and Schardl, 1997). Some of the *Epichloë* endophytes have found to produce a cryptic but infective conidial state on the surfaces of leaf blades (Tadych et al., 2014).

Endophyte-Host Interaction: Endophytes benefit the host plant by preventing them from pathogenic and parasitic organisms which tend to colonize into the host body (Zabalgogeazcoa, 2008). Colonization of endophytes into the plant tissue creates a "barrier effect", where the local endophytes outcompete and prevent pathogenic organisms from taking hold (Moy et al., 2000).

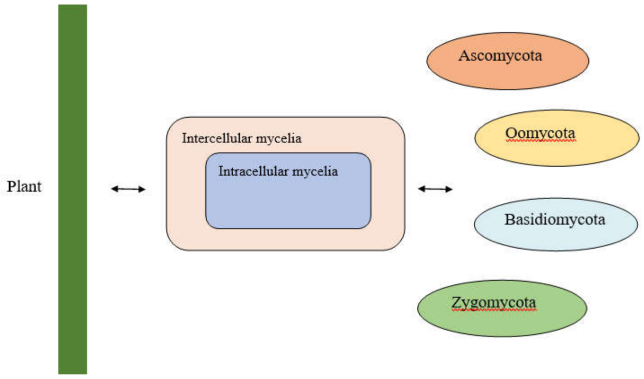

Figure 1. Existence of different endophytic fungi

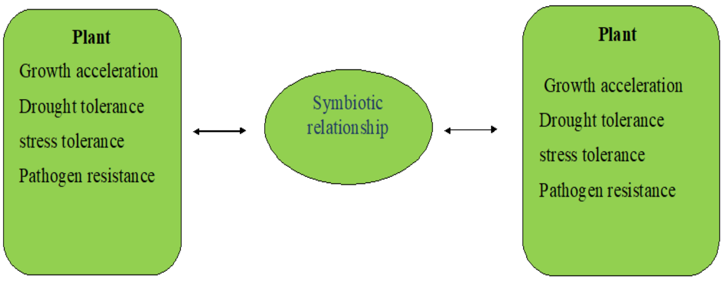

Figure 2. Relationship of a host plant and endophytic fungi

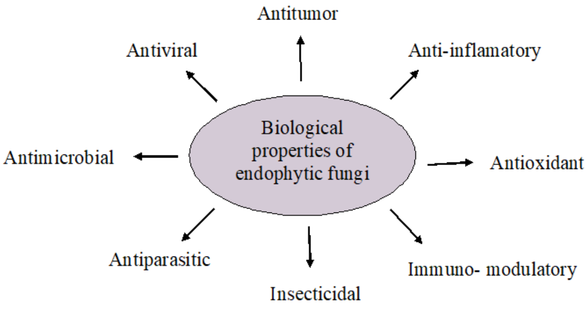

Figure 3. Different biological properties of endophytic fungi

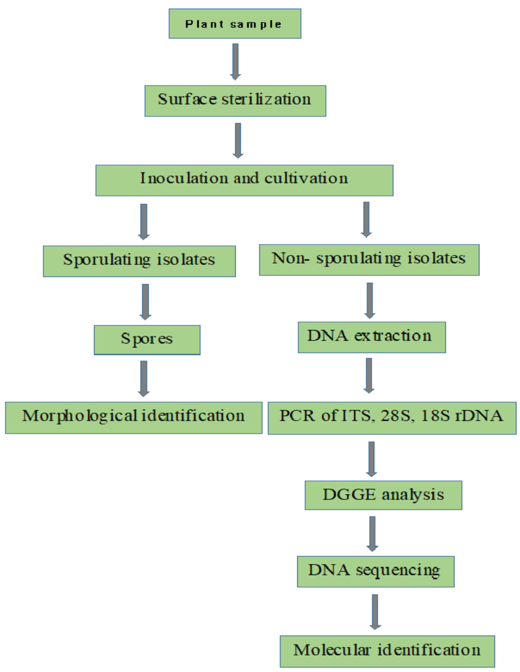

Figure 4. Schematic representation of fungal identification

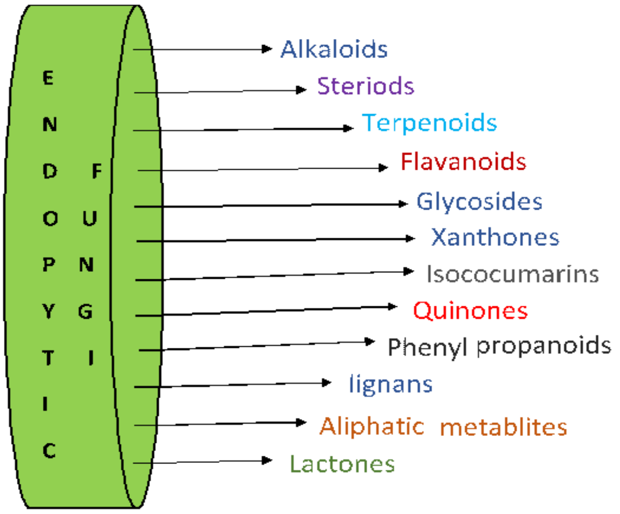

Figure 5. Different types of secondary metabolites produced by endophytic fungi

Schardl et al. (2013) found that Epichloae which includes *Epichloë* and *Neotyphodium* species who act as systemic symbionts of cool season grasses have the capability to produce alkaloid cluster of genes for biosynthesis of ergot alkaloids (EAS), indole-diterpenes (IDT) and Iolines (LOL) which help combat herbivory by vertebrates and invertebrates. Yue et al. (2000) purified fungal inhibitors from *Epichloe¨ festucae* and isolated indole derivatives, sesquiterpene, cyclonerodiol, and diacetamide and checked activity against *Cryphonectria parasitica.* The antifungal activity of Cyclonerodiol showed potent activity compared to others. Diacetamide which is a small size compound was found to produce in abundant quantity and was thought to provide inexpensive means of defending its host. According to Aly et al. (2011), an endophyte-host relationship is a balanced symbiotic continuum ranging from mutualism through commensalism to parasitism. Few endophytic fungi are latent pathogens and become active under suitable environmental conditions or when the host plant faces stress conditions (Petrini, 1991). Studies have shown that *Piriformospora indica* which is a root fungal endophyte induces salt tolerance in Barley (Baltruschat et al., 2008) and drought tolerance in Chinese cabbage plants (Sun et al., 2014).

It was also found that rice plants can exhibit cold tolerance via symbiosis with fungal endophytes (Redman et al., 2011). Some fungal endophytes have proven to increase plant growth and improve overall plant hardiness (Hardoim et al., 2008). The presence of fungal endophytes can cause higher rates of water loss in leaves (White et al., 1993a). However, certain endophytes may also help plants to tolerate biotic stress such as root herbivory (Cosme et al., 2016)or abiotic stresses, including salt, drought or heat stresses. Endophytes have also been shown to enhance plant development and increase nutrient (phosphorus and nitrogen) uptake into plants (Paungfoo-Lonhienne et al., 2010). Many reports have shown the benefits of endophytes and the relationship between endophytes and hosts which is considered to have a balanced antagonism with positive and negative effects on host depending on environmental conditions (Saikkonen et al., 1998). Redman et al. (2011) proposed the hypothesis of 'habitat adapted symbiosis' where plants are associated with particular endophytes that increase tolerance or resistance to the predominant biotic or abiotic stresses. Fungal endophytes may comprise functional communities in plants that increase a plant's capacity to survive and thrive in its habitat.

Endophytes for Agricultural Application: According to the studies endophytes can have many promising applications and can be used in agriculture to increase crop production by making it grow faster and more resistant than crops lacking endophytes (Gond et al., 2015). Few endophytes work under biotic and abiotic conditions, *Epichloë* endophyte is commercially used in turf grasses as it enhances the performance of the turf and is resistance against stress conditions (Meyer et al., 2013). In few studies, it was observed that *Piriformospora indica* a fungal endophyte of order Sebacinales, colonizes root and maintains a symbiotic relationship with many plants and has shown an increase in crop yield for a variety of crops such as in barley, tomato, maize, etc. It also provides protection to plant against pathogens and abiotic stresses (Waller et al., 2005).As per various evidence, it was found that fungal endophytes may work in functional consortia which helps to promote plant growth and also protects plants in a natural population, whereas plants in intensive cultivation may lose these defensive and growth promotional microbiome (Santhanam et al., 2015). Redman et al. (2011) studies that endophyte such as *Fusarium culmorum* and *Curvulari protuberate* significantly increases the growth of seedlings and increases stress tolerance in rice so, restoration of such endophyte in agricultural crops could result in the reduction of agrochemical inputs to control pests and diseases. This raises the possibility that crops could one day carry probiotic endophytes thus helping humankind to have a better life by increasing their health.

Properties of Endophytic Fungi: A single plant harbors thousands of endophytes into itself which is thought to be useful for mankind thus exhibiting different properties as antitumor, anti-inflammatory, antioxidant, immunomodulatory, insecticidal, antiparasitic, antimicrobial and antiviral activity (Kaul et al., 2012). For example, a renowned anticancer drug Taxol, which is also known as paclitaxel isolated from endophytic fungi *Taxomyces andreane* (Stierle et al., 1993) is used to treat ovarian and breast cancer (Cremasco et al., 2009) also Ergoflavin an anticancer agent isolated from leaf of *Mimusops elengi* which is an Indian medicinal plant (Deshmukh et al., 2009) exhibits good cytotoxic activity on HL60 and K562 cells by inducing apoptosis in leukemia cells (Zhang et al., 2009).

Harper et al. (2003) studied antifungal and antioxidant activity of *Pestalotiopsis microspore* an endophytic fungus that produces 1,3 dihydroisobenzofuran (Pestacin) which exhibits activity against *Pythium ultimum.* Zhao et al. (2012) in their study found a strong antioxidant activity of *Fusarium* endophyte isolated from pigeon pea that produced cajaninstilbene acid (CSA). Similarly, strong antioxidant activity was shown by *Xylaria* sp. endophytic fungi isolated from *Ginkgo biloba (Liu et al., 2007).* Lee et al. (1995) isolated two important immunosuppressive compounds Subglutnol A and Subglutanol B from *Fusarium subglutinans*, inhabiting *Tripterygium wilfordii*, which can be used to prevent allograft rejection in patients and in future can be used in autoimmune diseases. Another immunosuppressive fungal metabolite cyclosporine A which has been reported to be produced by Penicillium, Aspergillus, Byssochyamys, Septoria species is a potent drug used for the treatment of autoimmune diseases and organ transplantations (Bentley, 2000; Larsen et al., 2005). A study showed the insecticidal activity of an endophytic fungus against *Cephus cinctus,* a major local crop pest. In their study, it was found that *Muscodor vitigenus* isolated from liana growing in upper Amazon produces naphthalene under certain culture conditions which act as an insect repellent (Daisy et al., 2002a; Daisy et al., 2002b). Nodulisporic acid isolated from *Nodulisporium* sp. endophytic in *Bontia daphnoides* shows insecticidal activity against blowfly larvae (Demain, 2000). Hemtasin et al. (2011) in their study found antimalarial activity of *Phomopsis archeri* an endophytic fungus of *Vanilla albindia* which producesaromatic sesquiterpenes-phomoarchinis A-C which show activity against *Plasmodium falciparum.* Martínez-Luis et al. (2008)found antileishmanial activity from *Edenia* sp. which is an endophytic fungus that was isolated from the leaf of *Petrea volubilis* L. Endophytic *Phoma* sp. isolated from different medical plants has been reported to have potent antimicrobial compounds, for example, α-tetrlone derivative (3S)-3,6,7-trihydroxy-α-tetrlone along with cercosporamide, β-sitosterol and trichodermin exhibited antifungal and antimicrobial activity against pathogenic fungi *Fusarium oxysporum, Rhizoctonia solani, Colletotrichum gleosporioides* and *Magnaporthe oryzae* and against pathogenic bacteria *Xanthomonas campestris* and *Xanthomonas oryzae* respectively (Wang et al., 2012).

Also, *Chloridium* sp., isolated from *Azadirachta indica* produces a highly functionalized naphthaquinone called javanicin which possesses strong antibacterial activity against *Pseudomonas* sp., (Kharwar et al., 2009). Li et al. (2008a)Li et al. (2008b) isolated Pestalotheol-C metabolite from *Pestalotiopsis theae* an endophytic fungus. This isolated metabolite showed anti-HIV properties. Isaka et al. (2001) isolated two xanthone dimers, phomoxanthone A and B, from *Phomopsis* sp. These compounds showed significant activity against *Plasmodium falciparum* and *Mycobacterium tuberculosis*. Bungihan et al. (2011) isolated two benzopyranones, diportheone A and B from endophytic fungi *Diaporthe* sp. isolated from leaves of*Pandanus amaryllifolius* which showed growth inhibition against *Mycobacterium tuberculosis*.

Techniques used in the endophytic study: Endophytes can be identified in various ways, through amplifying and sequencing a small piece of DNA (Chen et al., 2015). Whereas some endophytes can be cultured from their host plant in a suitable growth medium (Clark et al., 1983). An important step during culturing an endophyte is to surface sterilize the explant or plant tissue before placing it on to the culture medium (White and Bacon, 1994). Surface sterilization kills epiphytic organisms that are present on the surface of the tissue ensuring the growth of only endophytic microbes (Norse, 1972). Endophytic fungi can be recognized by two basic techniques; i.e., direct observation and cultivation dependent method. In the direct observation method, endophytic fungal structures are observed under light and electron microscope. Most endophytic fungi have hyphal structures, i.e. they lack spore producing bodies that cannot be found in the taxonomic category so, it is not commonly used in endophyte diversity studies (Deckert et al., 2001). There are many endophytes which fail to sporulate when cultured into the medium (White and Cole, 1986), such kind of unculturable endophyte species are analyzed through DNA based analysis (Thomas et al., 2008).

Morphologically endophytes are characterized based on their colour, texture and growth rate (Wang et al., 2005). Some grass endophyte in genus *Epichloë* can be seen in intracellular sinuous strands of hyphae under the microscope when stained with aniline blue (White and Bacon, 1994). As fungal identification by morphology is based on spore bearing structures, this makes identification of few endophytes challenging which have no spore bearing capability. Molecular techniques are used to overcome the problem of identification of unsporulated endophytes, such endophytes which fail to sporulate are termed as *Mycelia sterilia* (GUO et al., 2000). A fungal phylogeny is represented by DNA sequence analysis, as the 5.8S gene is highly conserved, it's been used to access phylogenetic relationships at higher taxonomic levels (Wang et al., 2005). Noncoding rDNA spacer regions are known as the internal transcribed spacer (ITS) region show sequence variation between closely related species (Wang et al., 2005). Thus, ITS is used for the detection and identification of fungi (Schoch et al., 2012). In a single round of Sanger DNA sequencing roughly 650 bp region is obtained having three sub-regions i.e., the spacers ITS1 and ITS2 and 5.8S gene, amongst which ITS1 and ITS2 are species specific making identification easy (Koljalg et al., 2005). Procedure of molecular study generally involves (1) extraction of fungal DNA from surface sterilized plant tissue, (2) amplification of DNA fragment using fungal specific primers such as, ITS, 28S and 18S genes (Morakotkarn et al., 2007), (3) separation of amplified products on denaturing gradient gel electrophoresis (DGGE) (Sun and Guo, 2012), (4) purification of amplified products, (5) sequencing of purified product, (5) obtained sequence is used as query sequence and searched from GenBank and EMBL to check sequence similarity and phylogenetic analysis (Wang et al., 2005).

Diversity of Fungal Endophytes: As per the research there any many endophytes useful to mankind, but since there are very few scientists working in this field, and since due to deforestation, environmental contamination and deforestation, there is loss of great biodiversity, because of which there are chances of losing endophytes before their utility is explored (Kandalepas et al., 2015). However, there is only a small minority of endophytes that have been characterized by diverse species. Generally, fungal endophytes are from phylum Ascomycota(Unterseher, 2011). Few endophytic fungal species are found in order Hypocreales and Xylariales of Sordariomycetes (Pyrenomycetes) class (Bacon and White, 2000). Even though taxonomically endophytes may be diverse, Rodriguez et al. classified the fungal endophytes into ecological categories or functional classes (2009).

Importance and need to explore new Endophytic Fungi: The endophyte bearing plant is often thought to grow faster due to the production of phytohormones thus becoming competitive and dominant in a particular environment. Since the endophytes enhance a plant body in different ways which makes them beneficial and therefore they are exploited for human use since they are derived naturally (Kaul et al., 2012). Endophytes are synergistic to their host and are known to prevent the host from certain fungi or pests by producing secondary metabolites in return demanding nutrition (Strobel and Daisy, 2003). As the endophyte resides within the plant body it creates a symbiotic relationship with the host thus supplying necessary nutrients and compounds required for the endophyte to complete its life cycle. Fungal endophytes produce natural products which have a broad spectrum of biological activity having broad spectrum of activity including which are grouped in several categories including; alkaloids, steroids, terpenoids, flavonoids, glycosides, xanthones, isocoumarins, quinones, phenylpropanoids, lignans, aliphatic metabolites, lactones etc. (Zhang et al., 2006). Unlike the host plant, many endophytes are able to survive under quite extreme and inhospitable conditions. Endophytes are considered as a poorly investigated group of microorganisms that represent an abundant and dependable source of bioactive and chemically novel compounds (Kaul et al., 2012). Various natural products are being produced by endophytic fungi possessing unique structures and bioactivities which offer enormous potential for exploitation in agriculture and industrial areas (Tan and Zou, 2001). Fermentation of endophytic fungi which have potent secondary metabolites and potential of producing such bioactive compounds has several advantages, like reproducible and dependable productivity. Such compounds can be grown in an ample amount in a fermenter and can be exploited commercially. Few changes in culture conditions which can be lead to change in biosynthetic pathways thus exploring new derivatives and analogs of novel compounds (Strobel et al., 2004). A most important application of these endophytes is to utilize the secondary metabolites which are originally produced by plants. This application can open a completely new dimension to produce natural medicines in an extremely effective manner, thus understanding the relationship between endophytic fungi and their host medicinal plants.

Conclusion

The endophytic fungi are a good source for bioactive compounds and had a great demand for new drug development. Thus there is a need to exploit such endophytic fungi that are associated with medicinal plants. Fungal endophytes have diverse groups of species that vary in symbiotic and ecological functions. Most of the investigations are restricted to the level of fungal identification and bioactive assay. Since very few structures of bioactive compounds are characterized and identified, most of the hidden microorganisms are yet to be discovered and can lead to novel findings which will be rich and reliable sources of novel compounds with huge medicinal and agricultural importance. Since limitations for basic identification may create a hindrance in exploring a new fungus, molecular identification in this field may lead to better and quick recognition of particular host gene carrying endophytes. Many endophytic fungi carrying potent bioactive compounds have shown promising potential and usefulness in human health concerns. Discovering new bioactive compounds from naturally derived products are not only useful but more promising for formulating new drugs. The use of modern biotechnology such as genetic engineering, metabolic technology, and fermentation process can lead to better understanding and manipulation of such important microorganisms thus making them more beneficial for mankind.

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