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Endophytes: A hidden treasure inside plant

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Abstract
Nowdays, bioactive compounds gaining importance in pharmaceutical and agriculture industry due to their multitasking role in human and plant health. Endophytic microorganisms have a unique property to synthesize bioactive compounds having negative effect on plant and human pathogens. In the last few years, many bioactive compounds with insecticidal, antimicrobial and anticancer properties are discovered from endophytes by eminent scientist of the world. Bioactive compounds produced by endophytes alone or in conjunction with host plant have ecofriendly nature, toxic for pathogens and harmless for plant, animals and humans.
Bioactive compounds of endophytes are secondary metabolite of valuable biotechnological application, inoculation of these compounds or sole microbial inoculation improves plant health. Enzymes produced by endophytes help plant to develop systematic resistance against invading pathogens. Endophyte inoculation in plant triggers production of plant growth hormone which play essential role in plant growth and development. Endophytes also play an important role in abiotic stress management and helpful for plant to withstand during drought and salt stress conditions. The high diversity and their adaptation to various stress condition, untapped sources of bioactive compounds, effectiveness and ecofriendly nature makes it suitable candidate to use in sustainable agriculture production and in pharmaceutical industries. The present review emphasize on bioactive compounds of endophytes and their role in agriculture and pharmaceutical industries.

Keywords: antimicrobial, bioactive compounds, endophytes, phytohormones

Introduction

Endophytes are symbiotic microorganism lives inside the different tissue part of plant like nodule, root, bark, leaves and stems without causing any damage to plant or plant part. Approximately, 300000 higher plants present all over the world and every plant are accompanied with one or more endophytic microbes. Recent studies have revealed that endophytes associated with plant in a variety of relationship like mutualistic, commensalism, cooperation, pathogenic. In turn plant provides nutrient and shelter to the endophytic fungi. During mutualistic or symbiotic life cycle in plant endophytic fungi protect plant from drought, increased resistance to disease, protect plant from nematode attack and grazing, provide resistance to heat, and help in plant growth promotion. All of the symbiotic relationship of endophytes with plant is accompanied through production or secretion of bioactive compound. A chemical compound of biological origin possesses antimicrobial activity against other microorganisms of same and different species can be defined as low molecular weight compounds or bioactive compounds. These bioactive compounds are of different nature like terpenoids, steroids, xanthones, phenols, isocoumarins, perylene derivatives, quinines, furandiones, terpenoids, depsipeptides and cytochalasins. Endophytes have a resistance mechanism to overcome pathogenic invaders by producing secondary metabolites bearing antimicrobial activity. More than 8600 bioactive compounds have been reported from endophytes showed antimicrobial, anticancer, antiviral and antidiabetic properties. New organisms and many novel natural products from endophytic microbe can inhibit or kill a wide variety of harmful microorganisms like bacteria, fungi, viruses and protozoans that affect humans and animals. Endophytes do produce secondary metabolites in culture, but the temperature, composition of the medium and the degree of aeration will affect the amount and kind of compounds produced.

Endophytic microorganisms upon metabolomic investigations revealed that they are potential, reliable and promising source of novel organic natural metabolites exhibiting a wide range of promising bioactive properties viz. antioxidant, antimicrobial, enzyme inhibitive, antiparasitic, cytotoxic, immunosuppressive, neuroprotective, insulin mimetic and many more.

Due to the extreme medical importance of these metabolites, there is an increasing interest in studying fungal endophytes as alternative potential source of such useful functional metabolites. Therefore, keen studies on endophytes are required for the good and economical production of these metabolites from endophytic microbes as their production from host plant is comparatively costlier and time consuming. A wide range of endophytic applications have extensively been discussed by many researchers.

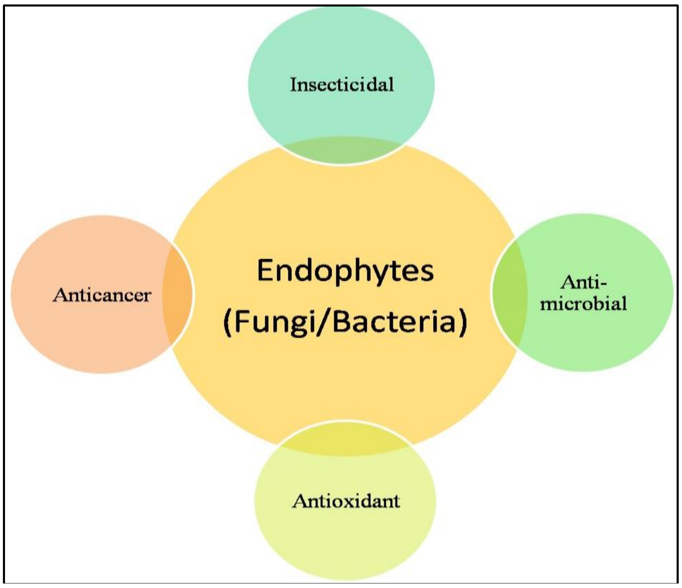

Fig 1: Use of various bioactive compounds of endophytes in different industries

So far, studies reported a large number of anti-microbial compounds isolated from endophytes, belonging to several structural classes like alkaloids, peptides, steroids, terpenoids, phenols, quinines and flavonoids. The three isolated compounds, melleolides K, L and M. from *Armillaria mellea* which showed anti-microbial activity against gram positive bacteria, yeast and fungi. Previously these antibacterial sesquiterpenoids, melleolides B-D, were yielded from *Armillaria mellea* were isolated by Arnone. A compound polyketide citrinin produced by endophytic fungus *Penicillium janthinellum* from fruits of Melia azedarach, presented 100% antibacterial activity against *Leishmania sp.* Podophyllotoxin (A non alkaloid lignin) and its analogues are clinically relevant mainly due to their antiviral and anticancer activities, further they are the precursors of many other useful anticancer drugs including etoposide and teniposide (Aly *et al*. 2013) [3]. Various novel microbial sources for podophyllotoxin include *Aspergillus fumigatus* isolated from *Juniperus communis*

Hence there is a need for naturally occurring compounds which are less toxic, target specific, easily degradable and can compete with synthetic pesticides. It is believed that screening of antimicrobial compound from endophytes is a promising way to overcome the increasing threat of drug resistant microbes of human and plant pathogen Here, we are covering the metabolites obtained from various endophytic microbes, belonging to various classes along with unidentified fungi and their potential as antifungal agent. Many of these compounds are shown in Table 1.

Distribution and diversity of endophytes

Almost all vascular plant species examined to date were found to harbor endophytic bacteria or fungi Surveys of various hosts during the past 20 years have demonstrated that the colonization of land plants by endophytes is ubiquitous. Endophytes are detected in plants growing in tropical, temperate and boreal forests with the hosts ranging from herbaceous plants in various habitats including extreme arctic, alpine and xeric environments to mesic, temperate and tropical forests. Moreover, the colonization of endophytes in marine algae, mosses, ferns, fern allies, numerous angiosperms, gymnosperms including tropical palms, broad leaved trees, estuarine plants, diverse herbaceous annuals, many deciduous and evergreen perennials has also been recorded. Endophytes are found in a wide variety of plant tissue types, such as seeds, ovules, fruits, stems, roots, leaves, tubers, buds, xylem, rachis and bark (Kaul *et al*. 2013) [12]. A perusal of the literature over the past decades indicated many ethnomedicinal plant species with rich botanical history, sampled from unique ecologica lniches and species are known to harbor potential endophytic microbes (Strobel and Daisy, 2003) [30]. There are approximately 300,000 different plant species on our planet. An estimate of 1 million endophytes seems reasonable if each individual higher plant hosts an average of one to few endophytic strains. As a matter of fact endophytes are important components of microbial biodiversity. Commonly, several to hundreds of endophytic species can be isolated from a single planta nd among them, at least one species showing host specificity. The environmental conditions under which the host is growing also effect the endophyte population and the endophyte profile may be more diversified in the tropical area. Endophytes are presumably ubiquitous in the plant kingdom with the population being dependent on host species and location. Many studies have tried to determine whether endophytes exhibit tissue-specificity or host-specificity but the results are contradictory with indications of both host-specificity and host generalism

Functions of endophytes

Some endophytes have no apparent effects on plant development and growth, live on compounds produced by plant, they are known as commensel endophytes. Some endophyte have beneficial effects on host plant such as production of plant growth hormones, protection against biotic stress by targeting invading pathogens, production of antibiotic against invading pathogens and induced systematic resistance inside host plant (Hardoim *et al* 2015) [9]. A third group of endophytes showed detrimental effect on plant. Generally, endophytes have neutral effect on plant during normal growth conditions while they are more beneficial and showed positive effect on plant during intensive condition during plant life cycle, in short during intensive condition endophytes acts like an army provide defence as well as need based requirement to the host plant (Verma *et al* 2009) [33]. e.g. fungus *Fusarium verticillioides* play both role as a pathogen as well as beneficial endophytes in maize. Same endophyte acts differently on different plant, for one plant acts in symbiotic manner for other plant acts in detrimental manner. Even for the same plant endophytes have different role, in one phase of life cycle become detrimental and in other stage of life cycle and harsh environmental condition become beneficial. The balance between two states is depends on type of species, but also depends on environmental conditions (abiotic stress). The behavior of endophytes inside plant host varies in different stages of life cycle. E.g. *F. verticillioides* repress growth of additional pathogenic fungus, Ustiagomaydis, protect their host from diseases. Clavicipitaceous fungi produced neurotoxic indole diterpenoid alkaloids in infected grass which leads intoxication in grazing cattles (Aly *et al* 2011) [2]. Some other compounds produce by endophytic fungi are provide defense against insect herbiovores (Verma *et al* 2009) [33].

Moreover, some studies suggested difference present on some part of antibacterial, antiviral antifungal and insecticidal compounds from fungal endophytes and some of these endophytes are pass on horizontally, and form like local infections within their hosts. Not all horizontally transfer fungal endophytes produced beneficial compounds, and suitable to the repeatedly small window having chances for ecology as well as functioning of positive endophytes (Higginbotham *et al* 2013) [10]. Various microbes especially bacteria and fungi, colonize inside the internal structure of specific host plant. Inside the host palnt endophytic microbes (both bacteria and fungus) interact with host plant as well as some nearby microbes. Endophytic arbsucular mycorrhizal fungi (AMF) form specialized structures called arbuscules where exchange of nutrients between fungus and host plant takes place. Plant derived carbon source exchanged with AMF derived essential nutrient of plant like phosphate (Pi), nitrogen (N) and potassium (K) elements. Plant derived cytoplasmic sucrose is transported to periarbuscular space where it is converted to hexose sugar (gluose). AMF derived important plant nutrient Pi and N are transported to fungal cytoplasm where it is converted to Pi and arginine. Phosphate (Pi) finally transported to host cytoplasm whereas arginine is initially converted to urea (Ur) and then to ammonium (NH_4). Some other important compounds of plant importance are also formed by AMF transported Nitrogen (N) like plant horomones i.e. auxins (IAA), cytokinins (CK), gibberellins (GA) and volatile organic compound having role in plant defense and development. Resistance in host plant is induced upon entery of enodphytic microbe because various microbial structure such as flagella, microbe derived proteins, pili, lipopolysaccharides of cell membrane, secretion system of endophytic microbes, various effectors and antibiotic molecule, jasomonic acid, salicylic acid of endophytic microbe origin triggers induced systematic resistance.

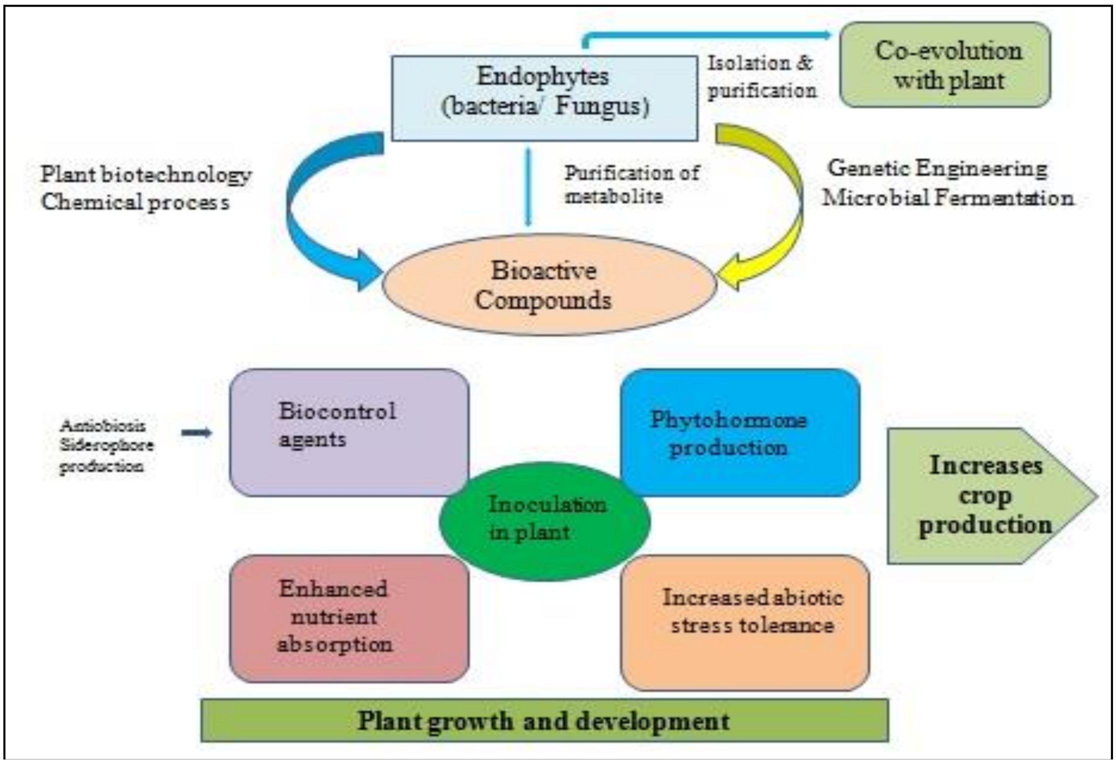

Fig 2: Schematic representation of endophyte isolation, purification and function of endophytes in host plant

Endophytes play an important role in defense system of plant. As life cycle of endophytes shorter than life cycle of host plant, so they develop in very large number inside the host plant, resultant in higher collection of antagonistic form that resistance against plant pathogens and harbiovores. Communications and interactions among large endophytic population brought through signal exchange via growth factors and antiobiotic molecule. Siderophore production by microbes causes sequestration of iron (Fe) molecule necessary for growth of plant pathogens. Therefore, this indirect mechanism of iron sequestration protects plant from pathogenic fungi attack (Hardoim *et al* 2015) [9] There is increasing evidences that at a suitable, interactions among valuable microbes and plants cause an immune response in plants similar to that of pathogens but later on, mutualists run away host defense responses as well they are able to successfully colonize plants (Aly *et al* 2011) [2]

Anti-microbial effect of endophytes

Bioactive metabolites are those low molecular weight organic molecule which are produced by microorganisms that are active at low concentration against other microorganisms (Guo *et al*. 2008) [18]. Endophytic microbes produced secondary metabolites active against pathogenic microbes (Tan and Zou, 2001). In the previous studies, it was reported that a large number of bioactive compounds isolated from endophytes, belonging to different classes like peptides, steroids, terpenoids, phenols, alkaloids, quinines and flavones (Yu *et al*., 2010) [36]. Extraction of novel antibiotic metabolites from endophytes is an alternative reduced the increasing level of drug resistance in pathogens. Till date a fewer effective antibiotic are discovered against a wide range of pathogens, less target specificity probably leads to unfavorable return on investment (Yu *et al*., 2010; Song, 2008) [36, 29]. The antimicrobial compounds are not only used as drugs for human kind but can also used to control food borne diseases and food spoilage, a serious issue nowdays (Liu *et al*., 2008) [18].

Many bioactive compounds are isolated from different endophytic microbe present on different host shows antifungal activities e.g. *Xyleria sp.* Isolated from different host such as sordaricin shows antifungal activity against *Candida albicans.* Similarly, bioactive metabolite mellisol, 1, 8-dihydroxynapthol 1-o-a-glucopyranoside had activity against herpes simplex virus (Pittayakhajonwut *et al*., 2005) [22]. The bioactive compounds isolated from endophytic fungus *Xyleria sp* YX-28 isolated from *Ginkgo biloba* L. plant was identified as 7-amino-4 methylcomurin. This compounds had a broad spectrum inhibitory activity against several food borne and food spoilage microorganisms including *E. coli*, *S.typhimurium*, *S. aureus*, *Yersinia sp*., *Shigella sp*, *V hameolyticus*., *V. parahemolyticus*, *C.albicans* and *A.niger* (Liu *et al*., 2008) [18]. Another strain of endophytic fungus Xyleria sp. Isolated from Abiesholophylla was characterized as a producer of griseofulvin, antifungal antibiotic use gainst treatment of human and animal skin diseases (Park *et al*., 2005) [21]. Further studies revealed high antifungal activity of endophytic fungus *Xyleria sp*. producing griseofulvin against plant pathogenic fungi also. Another fungus *C. globosum* isolated from *Ginkgo biloba* producing Chaetomugilin A and D had antifungal activity (Qin *et al*., 2009) [24]. Compounds Cytosporone B and C were isolated from Phompsis sp. Endophytic fungus grown inside mangrove plant tissue showed antfungal activity against *C.albicans* and *F. oxysporum* with MIC value ranging from 32 to 64 mg Ml (Huang *et al*., 2008) [11]. Endophytic fungus present in inner tissue of *Quercus variabilis* possessed growth inhibition against a wide range of fungua and bacteria. A compound kown as brefledin A, a lactone produced from endophytic fungus *Cladosporium sp.* Shows most promising antifungal activity against different plant pathogenic fungus (Wang *et al*., 2007) [34].

An endophytic Streptomyces sp., from a fern-leaved grevillea (Grevilleapteridifolia) in Australia was described as a promising producer of novel antibiotics, kakadumycin A and echinomycin. Kakadumycin A is structurally related to echinomycin, a quinoxaline antibiotic and presents better bioactivity than echinomycin especially against Gram positive bacteria and impressive activity against the malarial parasite *Plasmodium falciparum* (Castillo *et al*., 2003) [5]. An endophytic fungus *Streptomyces sp*. produced a peptide antibiotic Coronamycin which is active against pythiacceous fungi, the human fungal pathogen Cryptococcus neoforrmans and the malerial parasite *Plasmodium falciparum*.

B. *pumilus* isolated from cassava cultivated by Amzon Indian tribes produced a lipopeptide named pumilacidin have antifungal activites. Two new bioactive metabolites, ethyl 2, 4-dihydroxy-5, 6-dimethylbenzoate and phomopsilactone were extracted from an endophytic fungus *Phomopsiscassiae* isolated from Cassia spectabilis and had strong antifungal activity against two phytopathogenic fungi, *Cladosporium cladosporioides* and *C. sphaerospermum* (Silva *et al*., 2005) [28]. The polyketidecitrinin produced by endophytic fungus *Penicillium janthinellum* from fruits of *Melia azedarach*, presented 100% antibacterial activity

Table 1: List of bioactive compounds and their function

Endophytes	Host plant	Compound	Function	References
Pestalotiopsis microspora	*Taxus taxifolia*	Torreyanic acid	antimicrobial	Lee *et al*. (1996) [16]
Trichoderma harzianum	*Ilex cornuta*	Trichodermin	Antimicrobial	Chen *et al*. (2007) [6]
Chloridium sp.	*Azadirachta indica* A Juss	Javanicin	antimicrobial activity against *P. aeruginosa* and *P. fluorescens* *Pythium ultimum, Phytophthora infestans,* *Botrytis cinerea,*	Kharwar *et al*. 2009
Phomopsis sp	*Erythrina cristagalli*	Isoflavonoids	Antimicrobial	Red *et al* 2011
Emercilla sp	*Aegiceras*	Aegiceras cornicaulatum	Antiviral	Zhangg *et al* 2011 [37]
Eupenicillium parvum	*Azadirachta indica*	azadirachtin A and B	natural insecticides	Kusari *et al*, 2011 [13]
Chaetomium chiversii C5-36-62	*Ephedra fasciculate*	Radicicol	Cyotoxic	Turbyville *et al* 2006 [32]
	Hypermecium perforatum	Hypercin	Antiviral	Kusari *et al* 2011[13]
Phomopsis sp	*Plumeria acuatifolia*	Terpeniods	Antimicrobial	Nithya *et al* 2010 [20]
Muscodor albus	*Cinnamomum zeglanicum*	1-butanol, 3-methyl-acetate	Antimicrobial	Strobel & Daisy, 2003 [30]
Nigrospora sp. YB-141	*Azadirachata indica*	Solanapyrone Nigrosporalactone Phomalactone		
Xyleria sp. YX		7-aamino-4-methylcoumrin	Antimicrobial	Xu *et al* 2007
Hormonema sp	*Juniperus communis L*	Enfumafungin	Antifungal activity against *C. albicans*	Aly *et al*. 2011[2]
Eupenicillium sp.	*Xanthium sibiricum*	Eupenicinicols A and B	Antibacterial	Li *et al*. 2014
Cochliobolus sp.(UFMGCB-555)	*Piptadenia adiantoides*	Cochlioquinone A, Isocochlioquinone A.	Anti-parasitical Properties	Campos *et al* 2008
Gastrodia Elata	*Armillari amellea*	*Sesquiterpene aryl* esters	Antimicrobial activity	
B. pumilus MAIIIM4a	*cassava*	Pumilacidin	inhibitory activity against the fungi	Melo *et al*. 2009

			Rhizoctonia solani, Pythiumaphanidermatum and *Sclerotium rolfsii*	
Colletotrichum gloeosporioides	*Artemisia mongolica*	Colletotric acid	Antimicrobial	
Xylaria sp.	*Piper aduncum*	Phomenone	Antimicrobial	Silva *et al*. (2010) [28]
Herbaspirillum seropedicae	*Grass crops*	Serobactin A, B, C	Antimicrobial	Rosconi *et al*. (2013) [26]
Penicillium spp	*Azadirachta indica*	saponins, flavonoids and phenols	antibacterial and antifungal activities	Abubakar *et al* 2017 [1]

Conclusion

Endophytes are a poorly investigated group of microorganisms capable of synthesizing bioactive compounds that can be used to combat numerous pathogens. These have been dependable sources of bioactive and chemically novel compounds and have proven to be useful for novel drug discovery. Biotransformation, methods have a wide range of uses, particularly in the production of numerous bioactive compounds, as antimicrobial (vanillin, essential oils), antifungal and antiviral (alkaloids), antioxidant (eugenol), antiinflammatory (cineole) etc. Moreover, endophytes are good candidate for plant growth promotion in various crops through their various effects on plants like phytohormone production, nutrient absorption, and tolerance to biotic and abiotic stress. It is imperative to review and highlight the previous successes, on- going research and latest developments in research associated with endophytic microorganisms to draw the attention of the research community toward this emerging field and possible exploitation of the available sources for their therapeutic uses in various fields, such as the medical, pharmaceutical, food and cosmetics.

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