Production of Bioactive Secondary Metabolites from Endophytic fungi

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Abstract - *Endophytic fungi are the main sources for the production of secondary metabolites. They live asymptomatically inside the tissues of higher plant. Many important bioactive compounds have been effectively discovered from endophytic fungi having cytotoxic, antimicrobial, insecticidal, and anticancer and antioxidant activities. This summary will shows the exclusivity of the endophytic fungi used for producing plant-derived bioactive compounds such as antimicrobial compound, paclitaxel, Pestacin, isopestacin, podophyllotoxin, camptothecine, hypericin etc. and their chemical structure.The symbiotic relations among the endophytic fungi and their host plants, promoting creation of these bioactive compounds. They encourage the production of secondary metabolites with a broad range of biological activities.*

***Key Words*: Endophytic Fungi, Secondary metabolites, bioactive compounds, biological activities.**

1. INTRODUCTION

Endophyte is one which resides in the tissues below the epidermal cell layers without causing any negative effects [1]. Studies have shown that nearly 300000 plant species to survive on earth, each individual plant is the host to one or more than one endophytes. The endophytes may live in plants above ground parts especially in leaves but can also be create living in intracellular gaps of roots, that is one of the main entry door for these Microorganisms. The endophytic colonization can be positive to mass plants. Both fungi and bacteria are the mainly common microbes alive as endophytes but the most often isolated are fungi. The term "endophyte" has in generally been used for fungi living within plants, but later on researchers realized that inner parts of plants might be colonized by bacteria as well [2]. Plants do not live only as single entities but closely associate with the microorganisms present in their neighborhood and particularly with living internally. The emergence of the More than 20,000 bioactive metabolites is of microbial origin. Fungi are between the most important groups of eukaryotic organisms that be well known used for producing many new metabolites which are openly used as drugs or function as lead structures for synthetic modifications [3,24]. Endophytes are capable of synthesizing bioactive agents that can be used by plants for defense against pathogens and motivating plant growth as well as useful for new drug discovery process. Endophytes are known to produce metabolites such as alkaloids, terpenoids, steroids, quinones, isocoumarin derivatives, flavanoids, phenols, phenolic acids, and peptides [4]. A few species make new antimicrobial agents (cryptocandin from Cryptosporiopsis quercina), other make potent anti-cancer compounds (taxol from Taxomyces andreanae) and so far others produce compounds that can be able to utilized industrially, such as enzymes as well as solvent Fungal endophytes were first defined by Anton de Bary in 1886 since microorganism so as to colonize internal tissues of stems and leaves. The relationship among the plant and its endophytes is symbiotic [5].

1.1 Significance of endophytic fungi

Endophytic fungi which live symbiotically with majority of plants are utilized as an roundabout defense nearby to herbivores[1].These are the latent sources of pharmaceutical leads and create novel bioactive metabolites such as antimicrobial, anticancer, and antiviral agents. The invention of taxol produce by endophytic fungi improved the importance of endophytes[3]. Taxol is a very functionalized diterpenoid, found in each yew (Taxus) tree [25]. Taxus is the world's first billion dollar anticancer drug and is used for the treatment of various cancer like ovarian and breast cancers and now it is also being used to treat a number of various human tissue propagating diseases as well[5,8]. Endophytes may improve growth by producing phytohormones without any disturbance of host nutrient uptake or stimulation of host nutrient metabolism [12]. They may enhance biomass by producing growth hormones or begin the host hormone production .They can protect their host plants from pathogens and from pests [6,3]. Endophytes can reduce herbivory by producing alkaloids toxic to insects and vertebrate .Endophytic fungi are also capable of providing resistance to diseases. They help host plants to tolerate and withstand environmental stress such as drought, salts, and high temperatures. They play an important role in the ecological community, with the aim of decreasing the level of environmental degradation, loss of biodiversity, spoilage of land and water caused by excessive toxic organic insecticide, industrial sewage, and poisonous gases. Biological control using endophytes is a new method used in environmental remediation and in killing insects or pathogens [9,10]. Endophytic microorganisms are able to produce many enzymes so they might be used as biocatalysts in the chemical transformation of natural products and drugs because of their ability to alter chemical structures with a high degree of stereospecificity and to produce novel enzymes that facilitates the production of compounds of interest. Endophytic fungi as novel sources of anticancer lead molecules. Endophytic fungi helps in Plant Growth Promotion and Protection against Biotic and Abiotic Stresses [11]. Endophytic fungi have been accepted as a promising source of new pharmacologically active secondary metabolites that may be suitable for medicinal or agrochemical applications. They are one of the most unfamiliar and diverse group of organisms having symbiotic associations with higher life forms and may produce beneficial substances for host. Some endophytic fungi have developed the ability to generate related bioactive substances as those originated from the host plants such as paclitaxel, podophyllotoxin, camptothecine, vinblastine, hypericin and diosgenin which were also produced by their host plant [4, 29].

1.2 Advantage of endophytic fungi

Endophytic fungi having antimicrobial and other biological activities can produce wide range of natural products that is why they are used in drug manufacturing industries [6]. They are widely used for the production of antibiotics, vitamins, anticancer and cholesterol lowering drug. Fungi defend the plants from disease spreading agents and provide fundamental nutrients like phosphorous to the host plant for the process of senescence. The presence of soil in the fungi ensures healthy growth and also the development of plants and minerals. Favorable production of secondary metabolites that is biologically active result from metabolic interactions of endophytes with its host. Endophyte free plants are found to be much healthier than those infected with endophytes. In a microbe-plant relationship, endophytes contribute substances that have various types of bioactivity, such as antibacterial and antifungal. Many endophytic fungi stay quiescent within their hosts until it begins. Fungal endophytes can express relationships with different host including symbiotic, mutualistic, commensalistic and parasitic in response to host genotype and environmental factors [3]. The various fungal group might impact the ecology, fitness and shape of plant Communities, conferring resistance to abiotic (temperature, pH, osmotic pressure) and biotic (from bacteria, fungi, nematodes and insects) stresses [10].

1.3 Bioactive compounds from endophytic fungi

The symbiotic relationship among endophytic fungi as well as plants gives endophytes the powerful capability to produce new bioactive substances [4,28]. Endophytic fungi are an excellent source of secondary metabolites as a natural product [3].

2. Antimicrobial activity:

Endophytic fungi cut off a large number of metabolites live antimicrobial activity have been isolated from endophytic fungi [6, 7]. The compounds are present into several chemical structural groups like alkaloids, peptides, steroids, terpenoids, phenols, quinines and flavonoids [4,17]. They include compounds presenting antibacterial, antifungal and antiviral activities. Examples of antimicrobial agents having antifungal activity include cryptocandin cryptocin, ecomycins, pseudomycins, pestaloside and pestalopyrone [7].

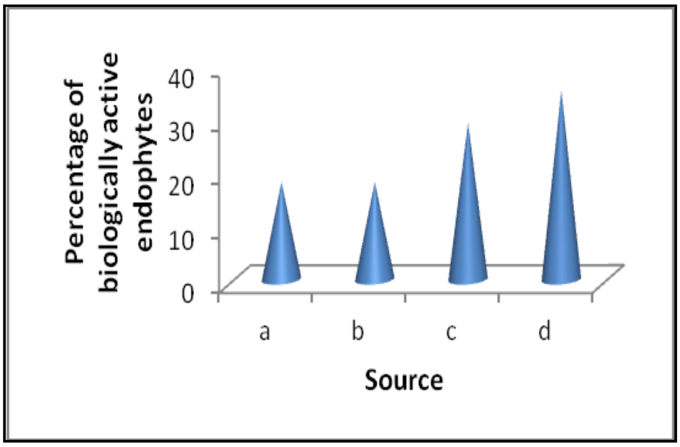
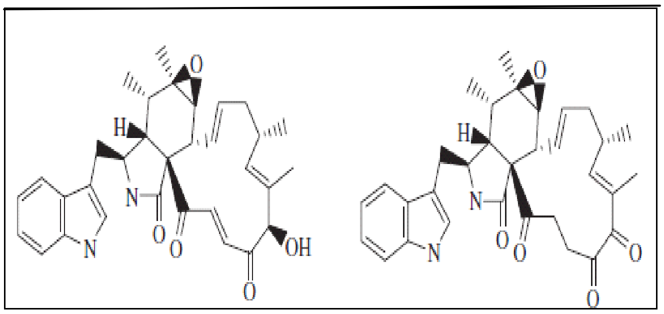


Fig -1: Proportion of biologically active endophytic fungal isolates from different sources with antimicrobial activities (31)

2.1 Alkaloids

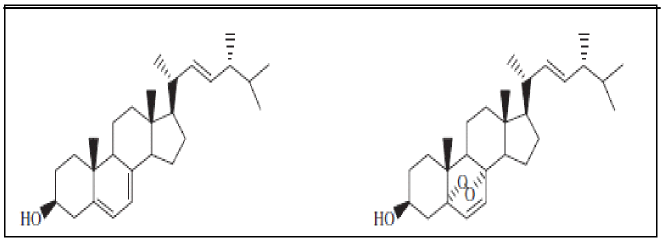
These are comparatively common secondary metabolites into endophytes and some of them show antimicrobial activities [14, 30]. Chaetoglobosins A and C were regarded since the culture of an endophytic C. globosum originating as of the leaves of Ginkgo biloba. These two metabolites are shown to be antibacterial next to Mucor miehei in agar diffusion technique. They have risky contact on mammals for showing significant toxicity towards brine shrimp larvae. Two newly reported antibiotics, pyrrocidinesA and B has been isolated commencing endophyte Acremoniumzeae in maize played important antifungal activity next to Aspergillus flavus and Fusarium Verticillioides [7].



ChaetoglobosinsA **Chaetoglobosin C**

2.2 Steroids

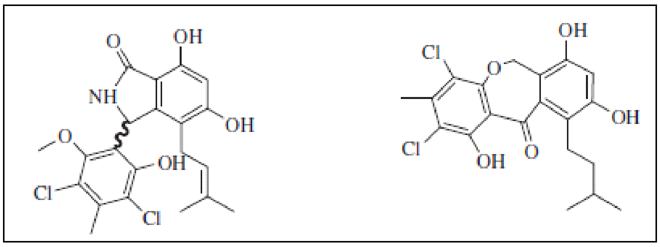
Antimicrobial Compound ergosterol and 5α,8α-epidioxyergosterol has been isolated from the culture extract of the endophytic fungus Nodulisporium sp. Most steroid compounds secluded from endophytes only showed temprate antimicrobial activities, so it is difficult to find efficient drugs or pesticides from endophyte [7].



Ergosterol **5α, 8α-epidioxyergosterol**

2.3 Phenols

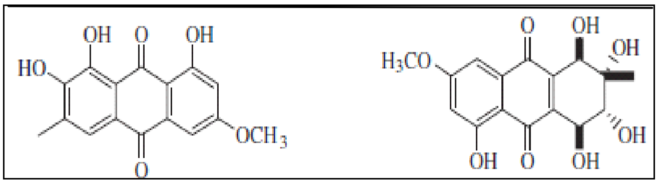
Phenol and phenolic acids can be isolated from endophytes cultures originating from a diversity of host plants [14]. Two new antibiotics pestalachlorideA and B have been isolated from endophytic Pestalotiopsisadusta which play a considerable antifungal activity next to three plant pathogens (Fusariumculmorum, Gibberellazeae and Verticilliumaiboatrum) [7].



PestalachlorideA **PestalachlorideB**

2.4 Quinones

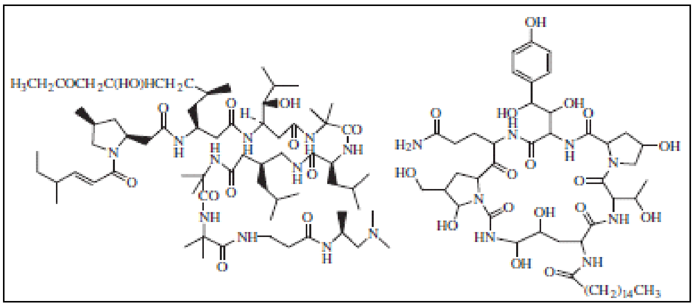
3-O-methylalaternin and Altersolanol A can be synthesized by Ampelomyces sp., an endophyte isolated since the medicinal plant Urospermumpicroides, shows antimicrobial activity next to the gram-positive pathogens, S. aureus, S.epidermidis and Enterococcus faecalis The antibacterial activity of Altersolanol A is perhaps not due to its cytotoxic activity. The compound acts like an electron acceptor into the bacterial membrane and inhibits bacterial growth [7].



3-o-methylalaternin **Altersolanol A**

2.5 Peptides

Many peptides formed by endophytes displayed important antimicrobial activities. LeuesnostatinA producedby Acremonium sp. in Taxus baccata displayed antimicrobial activity next to Pythium ultimum. Cryptocandin is a new peptide formed by endophytic Cryptosporiopsis quercina since Tripterigium wiflordii showed antibacterial activity against the C. Albicans. Cyclo(Pro-Thr) and cyclo(Pro-Tyr) were two of new antibacterial constituents formed by the fermentation broth of endophytic fungus Penicillium sp. secluded from mangrove plant Acrostichumaureurm [7].



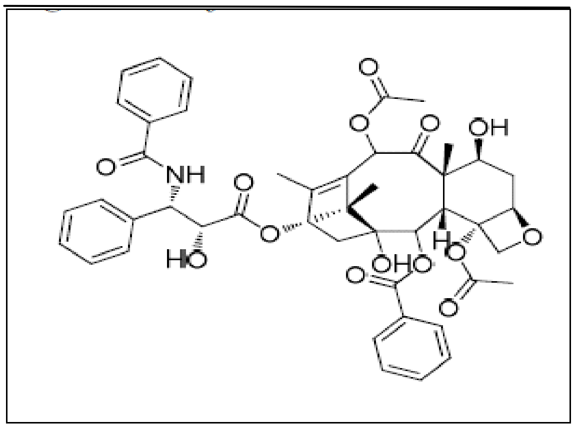
Leuesnostatin A **Cryptocandin**

3. Anticancer activity:

In the view of discovering novel and important naturally occurring anticancer compound, plant endophytic fungi have been recognized as an important source of biologically active secondary metabolites. The compounds generally secreted from endophytic fungi are cytotoxic in nature [33]. Till now almost 50 different fungal species have been identified producing one hundred anticancer compounds. Almost 19 different chemical classes of fungal secondary metabolites have been indentified and reported to possess anticancer properties on 45 different cell lines of endophytic fungi. 57% of all the isolated secondary metabolites of endophytic fungi were novel compounds. Till date, there has been incessant augment in the number of anticancer compounds isolated from endophytic fungi [34].

3.1 Paclitaxel

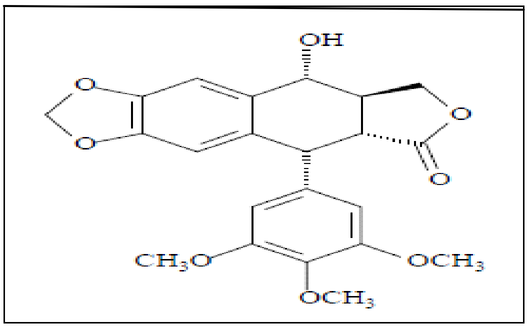
Paclitaxel (taxol) is a familiar and greatly functionalized tetracyclic diterpenoid bioactive compound originates initially from the bark of *Taxus brevifolia* in 1971and were proved with an efficient action next to prostate, ovarian, breast and lung cancers. Its primary method of action is related to the ability to become stable the microtubules and to disturb their dynamic equilibrium [15,18]. Paclitaxel is establish in extremely low amounts in various parts like the needles, barks as well as roots of *Taxus* species [3].



Paclitaxel

3.2 Podophyllotoxin

Podophyllotoxin (PDT) is an aryltetralin lignan having important anticancer, antiviral, antioxidant, antibacterial, immunostimulation as well as antirheumatic properties. PDT was used as a precursor used for chemical synthesis of the anticancer drugs such as etoposide, teniposide and etopophose phosphate. At present the main contributer of podophyllotoxin is from the natural *Sinopodophyllum* plants [4].



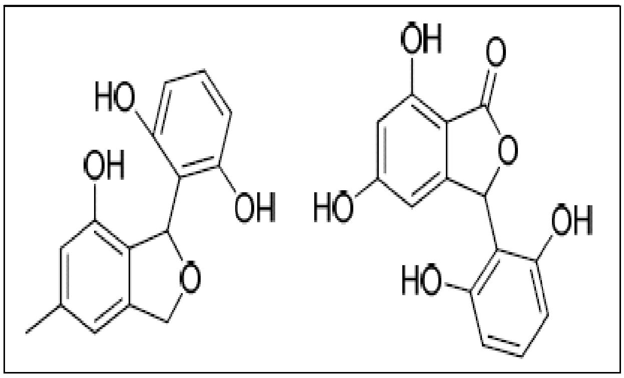
Podophylotoxin

4. Antioxidant Agents from Endophytes

The compounds containing antioxidant activity be highly effective adjacent to damage caused in reactive oxygen species (ROSs) and oxygen-derived free radicals, which add to a diversity of pathological effects, DNA damages carcinogenesis, as well as cellular degeneration[22,23]. Antioxidants were measured promising therapy for prevention as well as treatment of ROS-linked diseases as cancer, cardiovascular disease, atherosclerosis, hyper-tension ischemia/reperfusion injury, diabetes mellitus, neurodegenerative diseases, rheumatoid arthritis, and also ageing. Fungal endophytes linked with higher plants emerge to be a good source of new antioxidants.

4.1 Pestacin

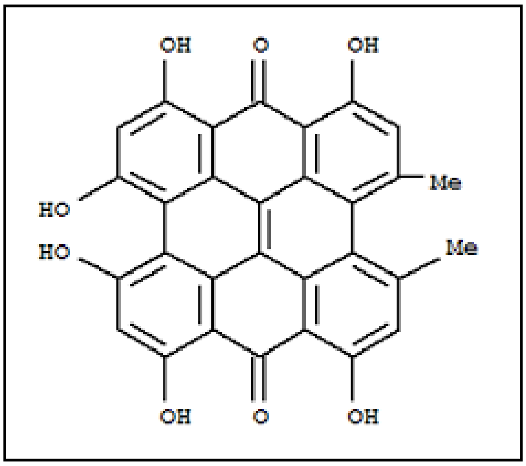
Pestacin and isopestacin be a compounds playing important antioxidant activity and as well antioxidant activity, pestacin and isopestacin also illustrate antimycotic and antifungal activities [5, 26].



Pestacin **Isopestacin**

4.2 Hypericin

Hypericin (2, 2'-dimethyl-4, 4', 5, 5', 7, 7'-hexahydroxy-mesonaphtodianthrone) be a Naphthodianthrone derivative. It is copied from plant containing high medicinal value. It is a main constituents of *Hypericum* species. It is also isolated from the medicinal herb *Hypericum perforatum* L.which also contain therapeutic efficiency[8].Their major constituents be napthodianthrones, mainly represented by hypericin,pseudohypericin, protohypericin, protopseudophypericin, the anthraquinone emodin. Hypericin were also use as an antidepressant suitable to its monoamine oxidase (MAO) inhibiting capacity, having effects comparable to bupropion. Possible uses of hypericin broaden to enhanced injury healing, anti-inflammatory effects, antimicrobial and antioxidant activity, sinusitis relief, as well as seasonal affective disorder [4].



Hypericin

5. Functions of endophytes

Some endophytes contain no apparent effects resting on plant performance but live on the metabolites formed by the host. These are known as commensal endophytes, while other endophytes confer special effects to the plant, such as protection next to invading pathogens and (arthropod) herbivores, also via antibiosis or via induced resistance, as well as plant growth promotion showing in the figure [2]. A third group includes underlying pathogens. Basically, endophytes contain neutral or detrimental effects on the host plant below normal growth conditions, while they could be beneficial below more intense conditions or throughout unlike stages of the plant life cycle [13]. For example, the fungus Fusarium verticillioides, having a dual role, both as a pathogen as well as a beneficial endophyte in maize. The balance among these two states is dependent relatively on the host genotype, but also on nearby occurring abiotic stress factors so as to decrease host fitness, ensuing in deformation of the delicate balance and within the occurrence of disease symptoms into the plant and manufacturing of mycotoxins via the fungus. However, useful effects have also been confirmed for e.g., strains of the entophytic fungus *F. verticillioides* repress the growth of an additional pathogenic fungus, *Ustilago maydis*, shielding their host next to disease. Alkaloids formed by the clavicipitaceous fungi of grasses are along the best compounds formed by endophytes [19, 27]. For example, the neurotoxic indole-diterpenoid alkaloids, so called lolitrems, are required for intoxication of cattle grazing lying on the endophyte-infected grass. Some compounds, and as other alkaloids, are for defense of the plant adjacent to insect herbivores [13]. Furthrmore, some reports having difference present on the some part of antiviral, antibacterial, antifungal, and insecticidal compounds through 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 formed protective compounds, and suitable to the repeatedly small window having opportunity for Ecology as well as Functioning of Microbial Endophytes [21].

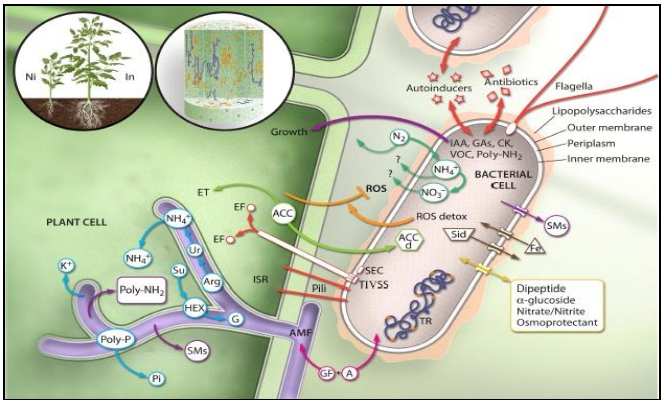


Figure shows: Beneficial properties of endophytes [2]. The left panel shows plants inoculated (In) with beneficial microorganisms that significantly improve plant growth compared to noninoculated (Ni) plants. Various microorganisms, in particular bacteria (orange) and fungi (purple), can colonize the internal tissues of the plant. Once inside the plant, the endophytic bacteria and fungi interact intimately with the plant cells and with surrounding microorganisms. Endophytic fungi, represented here as arbuscular mycorrhizal fungi (AMF) (lilac), might form specialized structures, called arbuscules, where plant derived carbon sources, mainly sucrose (Su), are exchanged for fungus-provided phosphate (Pi), nitrogen (NH4) and potassium (K) elements (blue). Plant cytoplasmic sucrose is transported to the periarbuscular space, where it is converted to hexose (HEX) to be assimilated by the fungus. Hexose is finally converted to glycogen (G) for long-distance transport. Phosphate and nitrogen are transported inside the fungal cytoplasm as polyphosphate granules (Poly-P), which are converted to Pi and arginine (Arg) in the arbuscule. Pi is transported to the host cytoplasm, whereas Arg is initially converted to urea (Ur) and then to ammonium (NH4) Fungal and bacterial plant hormones, such as auxins (IAA), gibberellins (GAs), cytokinins (CKs), volatile organic compounds (VOCs), and polyamines (Poly-NH2), as well as secondary metabolites (SMs), are transferred to the host (violet). Various bacterial structures, such as flagella, pili, secretion system machineries (e.g., TIV SS and SEC), and lipopolysaccharides, as well as bacterium-derived proteins and molecules, such as effectors (EF), auto inducers, and antibiotics, are detected by the host cells and trigger the induced systemic resistance (ISR) response (red). ACC, the direct precursor of ethylene (ET), is metabolized by bacteria via the enzyme ACC deaminase (ACCd), thus ameliorating abiotic stress (light green). A range of reactive oxygen species detoxification (ROS detox) enzymes might also ameliorate the plant-induced stress (orange). Diazotrophic bacterial endophytes are capable of fixing atmospheric nitrogen (N2) and might actively transport NH4 and nitrate (NO3%) to the host (dark green). Bacterial processes of siderophore production (Sid) and uptake (Fe) that are involved in plant growth promotion, biocontrol, and phytoremediation are shown in brown. Examples of various substrates on which the transmembrane proteins are enriched among endophytes are shown in yellow. Transcriptional regulators (TR) are also shown (orange). Communications and interactions between cells of microorganisms dwelling inside the plant tissues are promoted by growth factor (GF), antibiotic (A) (fuchsia), and auto inducer molecules [2].

Host plants	Endophytic fungi	Chemical compound	Reported activities*
Cinnamomum	zeglanicum Muscodor albus	1-butano,3-methylacetate	(a)
Ocimum basilicum	2L-5	Ergosterol, Cerevesterol	(a)
Ephedra fasciculate	Chaetomium chiversii C5-36-62	Radicicol	(b)
Erythrina cristagalli	Phomopsis sp.	isoflavonoids	(a)
Dictyosperma album	Pestalotiopsis adusta	Pestalachlorides	(c)
Plumeria acutifolia	Phomopsis sp.	Terpenoid	(a)
Ananas ananassoides	Muscodor crispans	propanoic acid, methyl ester,2-methylbutyl ester Ethanol	(d)
Aegiceras corniculatum	Emericella sp.	Aegiceras corniculatum	(e)
Guazuma ulmifolia	Muscodor albus	E-6 Caryophyllene, phenylethyl alcohol, 2-phenylethyl ester, bulnesene	(f)
Urospermum picroides	Ampelomyces sp.	3-Omethyl alaternin & ltersolanol A	(a)
Azadirachta indica A. Juss	Chloridium sp	Javanicin	(g)
Kennedia nigriscans	Streptomyces NRRL 30562	Munumbicin A,B,C and D	(a)
Cryptosporiopsi s quercina	Cryptosporiopsis sp.	Cryptocandin	(a)

Table 1: List of endophytic fungi producing plant secondary metabolites

*(a) Antimicrobial (b) Cytotoxic (c) Anti-fungal
(d) Anti-biotic (e) Anti-viral (f) Antibiotic (g) Antibacterial

6. Endophytic fungi help in Plant Growth Promotion and Protection against stresses

Endophytes play an important role in the defense systems of trees. Because life cycles of endophytes are measured to be much shorter than the life cycle of their host, they may develop faster in their host, resultant in higher collection of antagonistic forms that add to resistance short-living pathogens and herbivores. Endophytes may encourage plant defense reactions, so-called induced systemic resistance (ISR), important to a higher patience of pathogens [21]. There is increasing proof that at an promistage, interactions among valuable microorganisms 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. Bacterial factors dependable for ISR induction were identified to include flagella, antibiotics, *N*-acylhomoser lactones, salicylic acid, jasmonic acid, siderophores, and lipopolysaccharides [5].

7. Conclusion and future prospective

Plant endophytic fungi is a new and plentiful microorganism source having the special capability to form the similar compounds as well as other bioactive compounds obtained from their host plants have increased the interest in both basic research as well as applied fields. Scientists mainly determined on the study of endophytic fungal diversity, relationships among endophytic fungi as well as their host plants, looking for natural bioactive compounds obtained from the endophytic fungi. Many vital bioactive compounds with antimicrobial, insecticidal, cytotoxic, antioxidant and anticancer activities were effectively obtained from the endophytic fungi. They have great promising applications in agriculture and medicine. Several studies show that endophytes produce original secondary metabolites as a resistance mechanism to defeat pathogenic attack. It is thought that piercing for natural products formed by endophyte might be a able way to solve the problem that bacteria are appropriate resistant to some normally used drugs and assemble the emergency demand of discovering extremely effective, low toxicity, as well as no environmental impacted antibiotics to fight next to resistant bacterial species.

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