***Review Article***

**A short review on the co-evolution between Endophytic Fungi and their Host Plants**

**Abstract:**

Endophytic fungi are eukaryotic cells that have co-evolved with numerous plants for symbiotic and mutualistic association. Since centuries, these endophytic fungi are known to support and protect their host plants by secreting myriad forms of secondary metabolites. These secondary metabolites have been well studied for their roles as anti-cancer, anti-fungal, anti-inflammatory, anti-oxidative agent’s therapeutics. Additionally, these secondary metabolites provide defense against herbivory, upregulate nutrient and water uptake, and confer protection against wound and injury to the host plants. This review describes the factors involved between the co-evolution of endophytic fungi with their host plants; along with the implications of secondary metabolites in mediating cellular processes in host plants and as therapeutics.

**Keywords:**

Endophytic fungi, secondary metabolites, co-evolution, herbivory, antifungal, anticancer, anti-inflammatory, vertical transmission

**Introduction:**

Since several decades, evolutionary biologists have been fascinated with the co-evolution of prokaryotic cells like mitochondria and chloroplast with the eukaryotic cells. This revelation sparked the interest of many researchers to enquire about the co-evolution between various plants and other microbiota thriving within their ecosystems (Gray, 2017; Roberts, 2017). It was hypothesized that, around 1.5 billion years ago the mitochondria and Archaea have merged with eukaryotes for symbiotic and mutualistic reasons. Similarly, based on the fossil records it was hypothesized that around 400 million years ago several bacteria and fungi might have co-evolved with nearby plants for their benefit (Abdelfattah et al., 2021; Krings et al., 2007; Yeoh et al., 2017). After these discoveries, researchers globally have been studying the reason behind this co-evolution between the bacteria and fungus with plant cells. The current article focuses on co-evolution between fungus and plant cells, the possible reason and consequent effects observed between certain fungus and plants species, the pharmaceutical and agriculture-oriented benefits occurring as a result of this association.

A plant or tree species is known to thrive in the soil; that harbors numerous bacterial and fungal species, collectively called microbiota. The soil along with other environmental factors such as water, organic content, and pH determines the type of microbiota harboring near the plants species (Gopal & Gupta, 2016). Certain fungal species are a part of the microbiota found in the soil nearby plant roots. The fungal species compete with each other for space, resources, and survival. This competitive behavior might have led to a survival mechanism wherein certain fungal species thrive inside plant cells. Such fungal species are commonly known as ‘Endophytic Fungi’ (hereto referred as EF). Additionally, the soil microbiotas are selectively recruited by the plants based on their physiological, morphological and genetic traits (Bouffaud et al., 2014; Hassani et al., 2018; Yeoh et al., 2017).

**Co-evolution of EFs and host plants:**

Numerous studies have shed light on the involvement of seed in transferring EFs from generation to generation. This mode of transfer is commonly referred to as ‘Vertical transmission’ (parent to progeny). It is hypothesized that a myriad diversity of EFs is known to harbor inside the different parts of seeds, such as seed coat, endosperm, periplasm, and embryo. When the seed is placed in a suitable environment and germinates, the co-habiting EFs commences their growing phase. As the seed germination stages advances, the EFs begin to secrete their Secondary Metabolites (hereto referred as SM) in the developing seed parts. These SM aid in the overall seed development till the plant matures completely (Abdelfattah et al., 2021).

Additionally post germination, the EFs residing inside the seeds spread and grow inside their target plant parts such as leaves and roots. This provides the host plants with adequate protection against herbivory (in case of leaves) and aid in nutrient and essential metal uptake (in case of roots). Both these mechanisms (herbivory and aiding nutrient and mineral uptake) are mediated by the production of several SMs produced by EFs (discussed later in the article). These SMs are well studied in marine and mangrove derived EFs. Most of these metabolites have low molecular weights and do not affect the reproductive capability, growth, and development of the host plants (Alam et al., 2021).

**Role of EFs induced epigenetic modifications in evolution and physiology:**

Research shows that, the SM induce reprogramming of the host plants genome. Most of this genomic reprogramming is carried out via epigenetic modifications such as DNA methylation, DNA demethylation and histone modifications. These epigenetic modifications are mainly linked to improving host plant’s defense mechanisms, upregulating plants physiological functions, and improving the quality of secondary metabolites in different plant parts (Geng et al., 2019; Gupta et al., 2020; Strobel, 2018).

Most of the seed derived EFs are divided into two categories, namely transient and persistent/transmitted. The first category i.e. transient type consists of EFs that are not necessarily transmitted from parent to progeny via seedlings. These are more like temporary residents residing inside the host plants. Whereas, the second category i.e. transmitted types are transferred from one generation to other via seedlings and seeds. In a nutshell, when the seeds germinate, the EFs are predominantly found inside the plant and are able to grow and provide the host plants with the necessary chemicals / SMs that enable them to confer defense against pest and herbivory, provide disease resistance, upregulate nutrient acquisition, aid in indirect plant growth and development, and other vital cellular processes (**summarized in Figure 1**) (Abdelfattah et al., 2021).

It is also reviewed that, the SMs released by the host plants are able to activate gene expression via epigenetic modifications. These SMs are able to mimic certain established epigenetic chemical modifiers like sodium butyrate, 5-azacytidine, suberoylanilide hydroxamic acid, and valproic acid. These chemical modifiers are recognized for their involvement in DNA methylation and histone modifications. Based on few studies, *Leucostoma persoonia*, *Fusarium oxysporum*, *Pestalotiopsis crassiuscula*, *Aspergillus fumigatu*, *Penicillium herquei*, *Anteaglonium sp*. FL0768 and many more such EFs have been known to mimic the actions of established chemical epigenetic modifiers in host plants *Rhizophora mangle*, *Datura stramonium L*, *Fragaria chiloensis*, *Cordyceps sinensis*, *Fragaria chiloensi*, and *Selaginella Arenicola* (Beau et al., 2012; Chen et al., 2013; Guo et al., 2020; Mafezoli et al., 2018; Magotra et al., 2017; Yang et al., 2014). It is also known that epigenetic modifications are passed from one generation to the next during reproduction. In other sense, if the EFs are transmitted from one generation to the next, the eventual epigenetic modifications inducing secondary metabolite productions are also transmitted in similar manner (Feng & Jacobsen, 2011; K et al., 2023; Toghueo et al., 2020). Thus, paving a new path to investigate the EFs induced SMs production in their host plants. Wherein the medicinal properties of SMs can be overexpressed and harvested for treatment of various ailments in plants and humans.

**The different categories and classes of EFs evolved during the course of evolution:**

Based on the enormous biodiversity, these EFs have been divided in two major categories namely, Balansiaceous or Clavicipitaceous (C group) and non- Balansiaceous or Non- Clavicipitaceous (NC group) endophytes. The C group of endophytes are obligate endophytes that infect the host plants ovules, thus having a vertical transmission mode of infection. These endophytes are known to reside in the shoots and rhizomes of the host plants. Inside the host plants, the shoots and rhizomes are the primary site for herbivory by various vertebrates and invertebrates. The residing EFs have been speculated to produce SMs that confer protection against herbivory, aid in host plant survival during drought and other stress like conditions (Poveda, 2021; Roberts & Lindow, 2014).

While the NC group consist of EFs which are mainly passed from one host plant to other plant via ‘horizontal transmission’. These NC group EFs are found to reside in the aerial parts such as stem, roots, leaves, flowers, fruits and rhizomes of the host plants. These EFs usually stay in dormant state and become actively produce defensive SMs when the host plant is injured, wounded or infected by pathogens. Species belonging to EFs such as *Piriformospora* and *Fusarium* primarily demonstrate these cellular and physiological behavior in host plants (Mishra et al., 2021; Rodriguez & Redman, 2008; Rodriguez et al., 2008; Schulz et al., 2002).

Based on the two major categories, there are four main classes of EFs. Class 1 includes EFs that are transferred via vertical transmission, confer protection against drought related stress, aid in defence against herbivory from animals; by colonizing plant shoots and seeds (Clay, 1988; Saikkonen et al., 2002; Stone et al., 2004). While Class 2 are commonly called as mycorrhizal fungus, as they play vital role in upregulating nutrients and water for host plants. A very limited plants encompass Class 2 EFs in their plant parts (Rodriguez et al., 2008).

Class 3 can be recognised as NC group EFs. Owing to their horizontal transmission from one host plant to the other, they have been found to thrive in both non-vascular and vascular plants; along with angiosperms like woody and herbaceous plants found in tropical forests and antarctic regions (Davis et al., 2003; Higgins et al., 2007; Murali et al., 2007). Whereas Class 4 EFs are known as ‘Ascomycetous Fungi’. These Class 4 fungi are characterized by the presence of darkly melanized septa (confined to plant roots) in the inter and intracellular hyphae. Similar to Class 3, these Class 4 EFs occur in host plants found in antarctica, artic, alpine, subalpine, tropical and temperate ecosystems (Jalgaonwala et al., 2011; Jumpponen, 2001). Nonetheless, more endophytic fungal species are discovered globally that are yet to be classified under these categories and classes.

EFs have a wide variety of host plants such as ~200 angiosperms, gymnosperms, both annual herbaceous broad-leafed plants, ferns, mosses, liverworts, algae and many more. Additionally these plants are found in different habitats like artic, tropical and temperate forest, croplands, savannah, desert and grassland (Rashmi et al., 2019; Suryanarayanan et al., 2018). Thus, owing to the wide variety of environmental conditions, the plants have evolved according to the stressful conditions since generations. Studies have pointed that, plant adaptations to the environment is due to the SMs produced by the endophytic fungal species residing in each host plants (Mishra et al., 2014). Apart from the beneficial effects for host plants, plant derived SMs have attracted the attention of researchers worldwide. These SMs are known to have numerous biological functions. The next section discusses about the various SMs produced by EFs in their host plants; along with their biological functions as therapeutics.

**Certain SMs /allelochemicals isolated from EFs and their Biological functions:**

EFs are peculiar fungal species that have been studied to symbiotically and mutualistically thrive inside the plant cells. The EFs promote plant growth and development by producing SMs such as alkaloids, phenols, flavonoids, sterols, and terpenoids; thereby conferring anti-microbial activity, stress tolerance, nutrient solubilization, and provide defense against herbivory. In return, the plant cells have been studied to provide shelter and energy source to the EFs (Pan et al., 2017). The next section of this article will review various studies that demonstrated the beneficial roles of EFs in plant species.

The selective recruitment of EF has been studied to have a significant impact on the overall growth and development of the host plant species. For instance, two EF species *Talaromyces argentinensis* and *Aspergillus welwitschiae Ocstreb1* found in rice plant *Oryza coarctata* showed significant improvement in *in vitro* plant growth promoting abilities like nitrogen fixation, zinc solubilization. These fungal inoculates showed overall improvement in the siderophore, ACC-deaminase, and indole acetic acid production of *O. coarctata*. Moreover, these inoculates enhanced the metabolic turnover and chlorophyll content in *O. coarctata* seedlings. These plants were able to tolerate and exhibit growth in high soil salinity treatments of 900mM concentrations (Airin et al., 2023). Although this data showed remarkable improvement *in vitro*, the *in situ* biofertilizer capability of these inoculates in other plant species is still elusive.

A recent study investigated the variation in the biochemical and molecular properties of *Piriformospora indica* inoculated *Phoenix dactylifera* plant. This study aimed to identify the effect on the chlorophyll content, sodium and potassium ions concentration; along with fluctuation in antioxidant enzymes like catalase, peroxidase, and superoxide dismutase. Their findings suggested *P. dactylifera* growth promotion under normal and salt stress conditions. Sodium potassium ions homeostasis seedlings, enhancement in antioxidant enzyme activity. The study also demonstrated an increase in zinc and phosphate content of *P. dactylifera* roots and seedlings; apart from regulation of stress responsive genes such as PdHKT1;5, PdSOS1, PdRSA1, PdLEA2 (Sabeem et al., 2022). The study by Sabeem and group was aimed to access the plant growth potential on *P. dactylifera*, they were unable to measure the approximate salt tolerating capacity of the plant upon inoculation with *P. indica*. Thus, a study based on the different salt tolerating potential and the consequent effect on the levels of plant hormones (indole acetic acid and gibberellin) could shed light on the holistic effect of *P.indica* inoculation in medicinal and agricultural plants.

A non-conventional approach using the combinatorial interaction between *Piriformospora indica* and *Azotobacter chroococcum* was studied on *Artemisia annua L.* plant for salt stress analysis, enhancement of enzymatic/ non-enzymatic based antioxidant activity. This combinatorial treatment was able to ameliorate the induced deleterious effects of salinity (ranging from 0-200mM concentration) on *A. annua L.* plant. The study also showed a marked increase in the proline content of *A. annua L.* leaves, upregulated ascorbate, catalase, glutathione reductase, peroxidase, and superoxide dismutase activity. Along with this the combinatorial treatment triggered an increase in carotenoids, flavonoids, and phenolic content (Arora et al., 2020; Arora et al., 2016).

The possible explanation for this symbiotic behavior by EF may be due to the competitive behavior of EF against other fungal species. EFs have been studied to produce and secrete ‘Allelochemicals’ upon physical damage to host plants. According to the co-evolution hypothesis, these allelochemicals are known to inhibit the growth of other competitive fungal species; thereby demonstrating anti-microbial effects. Additionally, these allelochemicals nullify the toxic effects of their competitor fungal species. In contrast these allelochemicals provide specified volatile organic compounds to the host plants for their growth, aid in resistance during high salt concentration and drought conditions, along with defense against herbivory. To simplify, these allelochemicals can be categorized as SMs which predominantly exist in plants (Konarzewska et al., 2020; Poveda, 2021).



**Figure 1:** This figure summarizes the biological functions conferred by few endophytic fungi found to thrive in leaves and roots of plants.

In other terms, the SMs/allelochemicals secreted by these EFs are widely studied for their antibacterial, cytotoxicity, antiproliferative, anticancer, Treatment against Alzheimer’s disease, anti-inflammatory, and anti-oxidant efficacies as well (**summarized in Figure 1**) (Abdou et al., 2020; Dhakshinamoorthy et al., 2021; Khan et al., 2018; Mao et al., 2021; Okoye et al., 2013; Rodrigues de Carvalho et al., 2016; Sana et al., 2019; Seetharaman et al., 2017; Wen-Xia et al., 2020). To elaborate, a study conducted by Zhibo Hu and colleagues isolated and extracted ten allelochemicals from *Botryosphaeria ramose* (a mangrove fungus). From these ten compounds (Polyketides), 5,7-dihydroxy-3-hydroxymethyl-2-methylchromone, 5 hydroxy2,3dihydroxymethyl-7-methoxychromone, and 5-hydroxy-3-acetoxymethyl-2-methyl7- methoxychromone (types of chromones) were able to show anti-fungal activity against a plant pathogen’s (*Fusarium oxysporum, Fusarium graminearum, Penicillium italicum, and Colletotrichum musae*) (Hu et al., 2020). Thus, demonstrating anti-fungal activity and upregulating the host plant defense mechanism. Another EF called *Alternaria* species is known to comprise of allelochemicals that confer anticoagulant, anticancer, antioxidant, and antiparasitic effects (Hashad et al., 2021). This justifies the anti-fungal capability of allelochemicals secreted by EFs against their competitive species.

Five new cytochalasans (an alkaloid) extracted from *Diaporthe* (an EF) found in *Cyclosorus* fern showed potential tumor cells cytotoxicity upon inoculation with various perhydroisoindolone (Yang et al., 2020). Two erythritol derivatives named oxalicine and meroterpenoid-type alkaloid were extracted from *Penicillium chrysogenum* XNM-12 (marine algal-derived endophytic fungus) demonstrated moderate anti-bacterial and anti-fungal effects against plant pathogens *Alternaria alternata* and *Ralstonia solanacearum*. Therefore, demonstrating anti-microbial activity induced by EF derived allelochemicals.

Diaporpenoid A and Diaporpyrane A were two diterpenoids extracted from *Diaporthe* sp. QYM12 (a mangrove endophytic fungus). Among these two compounds, Diaporpyrane A demonstrated potent Anti-inflammatory activity against key inflammatory enzymes nitric oxide synthase and cyclooxygenase-2; as compared to Diaporpenoid A (Chen et al., 2021). Another diterpenoid Libertellenone T isolated and extracted from an endophytic fungus Phomopsis sp. S12. This compound inhibited the Interleukin-1b and Interleukin -6 induced inflammatory response generated by lipopolysaccharide (LPS) in macrophages (Xu et al., 2019). Thus, showing the potential anti-inflammatory activity by allelochemicals derived from certain EFs.

Together, these studies point towards opening an avenue for drug development by pharmaceutical companies. These allelochemicals are organically derived compounds and carry a natural tendency to interact with animal and plant cells. Thus, nullifying the concern of side effects observed by their counterparts i.e. synthetically derived drugs (Chinchilla et al., 2014; Singh et al., 2021).

**Conclusion:**

The production of SMs by EF in their respective host plants play a significant role in mediating defense against herbivory in plants, upregulating nutrient and water uptake by plants. Additionally, these metabolites have been studied to confer resistance in host plants against drought and salinity related stress. These host plants are known to thrive in myriad environmental conditions and habitat, thus pointing towards the evolutionary significance of EFs in plants. Together these metabolites and their various therapeutic properties have grabbed the attention of researchers on a global scale. These revelations warrant further studies in the field of cancer biology, agriculture, immunology, and other disease found to affect humans.

**Highlights:**

* Co-evolution of Endophytic fungi and host plants play prominent roles like providing the host plants with adequate protection against herbivory and aid in nutrient and essential metal uptake.
* There are numerous studies indicating the involvement of Endophytic fungi induced epigenetic modifications playing significant roles in in evolution and physiology.
* Different categories and classes of Endophytic fungi have developed during the course of evolution.
* Certain Secondary metabolites /allelochemicals isolated from Endophytic fungi have various biological functions such as antibacterial, cytotoxicity, antiproliferative, anticancer, and many more.

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