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Functional Importance of Endophytic Microorganisms in Plant Growth Promotion, Bioactive Compound Production for Sustainable Agriculture: A Review

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ABSTRACT

Endophytes constitute living microorganisms inhabiting inside tissues of plants. Endophytes perform critical functions in upgrading the growth of plants and their defense to fight stress by a variety of phytohormones, biologically active compounds, volatile organic compounds, and biotechnologically valuable enzymes. How biological nitrogen fixation, nutrient uptake, and disease suppression occurs by endophytes, have been discussed in detail in the review. The mutual symbiotic relationship enhances plant growth, fitness, physiology, and metabolite production ability. Endophytes inhibit the invasion of pathogenic microorganisms and protect crops against diseases. Endophytes are also involved in strategies for environmental clean-up such as biodegradation, bioremediation, and phytoremediation. Therefore, it is necessary to analyze and study the mechanisms of interactions, colonisation, diversity, and functionalities for successful implications in agriculture. Thus, the endophytic relationship opens possibilities for medicine, agriculture, and biotechnology. The present review emphasizes the importance of endophytes in sustainable agriculture under several adverse environmental impacts through a better understanding of their functioning inside the plant.

Keywords: Bioactive compounds; Biocontrol; Bioremediation; Biotic and abiotic stress; Endophytes; Secondary metabolites

1. INTRODUCTION

Climatic changes have a catastrophic effect on crops in the 21st century, constituting a growing threat to global food.[1] According to the FAO report (2016), climatic factors (e.g., higher temperature, frequent changes in weather events, water deficit, increase in sea levels, degradation of land, and loss of biodiversity) drastically affect agriculture's ability to meet the efforts in eradication of poverty, hunger, and malnutrition. Modern agricultural practices use unacceptable level of agrochemicals (for e.g., pesticides and fertilisers) which have adverse consequences on soil fertility, creates an ecological imbalance, contaminates groundwater, affects microbial communities, and alters the soil pH and human health.[2] Conventional breeding practices and genetic engineering techniques proved inefficient because many resources were spent on trailblasing protocols to identify and study such transgenics.[3] Therefore, an alternate eco-friendly strategy must be preferred for enhancing plant yield potential, pest and disease resistance, and improved performance. The microscopic organisms are used in agriculture to elevate soil productiveness, and expanded nutrient driving and productivity of crops.

Endophytes are beneficial microorganisms (actinomycetes, bacteria, or fungi) that live within plants, inter or intracellularly, causing no harm to them. They are an abundant source of a variety of secondary metabolites, phytochemical compounds, and green approaches to reducing the practice of agrochemicals.[4] Endophytes promote plant development by various mechanisms. Direct mechanisms for plant growth include the production of plant hormones like auxins, cytokinin, and gibberellins, nitrogen fixation, solubilisation of PO_4, and siderophores production. Indirectly endophytes increase competition for nutrients, and ecological niches and induce antimicrobial bioactive metabolites production[5]. Endophytes are bestowed with another remarkable potential to suppress diseases, improve phytoremediation efficacy, and help in stress alleviation.[6,7] Their interaction with their host plant increases specific responses against pathogenic attacks. These microorganisms can induce positive reactions against herbivore pests, synthesising important bioactive metabolites, improving tolerance to plant stress, and enhancing the immunity of plants.[8] More recently, Asian Development Bank (ADB) has also recognised fungal

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symbionts as 'climate adaptation technology' in improving stress responses that emerged from abiotic stressors[9]. Unlike chemical fertilisers, the endophytes serve as biofertilisers which have no repercussions on the climate, texture, and productivity of soils.[10]

2. COLONISATION OF ENDOPHYTES

Plants exhibit a close relationship with diverse microorganisms in various ecological niches. A plant host can be occupied by epiphytic, rhizospheric, and endophytic microorganisms. Among all these interactions endophytic interaction is most intimately associated with the plant host. The plant host's and its endophyte's relationship is often symbiotic.[11] Every living plant is colonised and inhabited by diversified species of endophytic microbes in a mutualistic and symbiotic manner. The colonisation of microbes starts with the initial communication signaling process providing the entry of microorganisms from soil to root. Endophytic microbes can get into plants either by vertical seeding technique or by horizontal transmission into the plants from the soil.[12]

Plant rhizospheric zone and root exudates led to the formation of compounds that function as chemo attractants.[13] This assists in the recruitment of microbes and communication between plant roots and microbes. As soon as chemotaxis occurs, endophytes migrate to the plant surface.[14] The next step is attachment facilitated by structural organelles/biomolecules (i.e., flagella, fimbriae, pili, lipopolysaccharides, and exopolysaccharides).[15]

Passive penetration in host tissue occurs when cracks open in the root zone or the stem, flowers, cotyledons, and leaves.[16] Endophytes can penetrate plants through stomata present on the surface of leaves and young stems, periderm of stems via lenticels, germinating radicals, and seeds.[17] Penetration and attachment may be achieved by acquiring biologically active compounds such as lytic enzymes (including cellulases) and lysozymes. Internal tissues of plants colonised by bacterial endophytes have different genomic organisation than rhizospheric bacteria.[18] Lateral gene transfer through plasmid or transposon may induce colonisation in plant.[19]

3. ACTINOBACTERIAL ENDOPHYTES IN SUSTAINABLE AGRICULTURE

These gram-positive microorganisms have high guanine and cytosine nucleotide base content with filamentous aerial mycelia producing luxurious bioactive compounds. These endophytes can act as antibiotics, antioxidants, enzymes, and as enzyme inhibitors.[20] They are found in extreme habitats such as arid zones, saline and aquatic ecosystems, caves, and in different environmental niches.[21]

Actinobacteria are equipped with multifunctional plant growth-promoting characteristics and impart beneficial properties to the host plant. They are involved in atmospheric N_2 fixation, siderophores, and IAA production facilitating ecological balance in soil system.[22] Actinobacteria are producers of antibiotic compounds and hydrolytic enzymes such as chitinases and glucanases. Endophytic actinobacteria

Table 1. Some endophytic actinobacteria in plant growth promotion and biocontrol of phytopathogen

Host plant	Endophytic actinobacteria	Mode of action	Reference
Zea mays	*Streptosporangium* sp. L21	Production of Glucoamylase	25-26
Artemisia herba alba	*Streptomyces* sp.	Biocontrol against *Botyris cinerata*	27
Cicer arietinum L	*Microbispora sp. CP56, Actinomadura sp. CP84B, Streptomyces spp. CP200B and CP21A*	positively affect many aspects of the chickpea-*Mesorhizobium* symbiosis and resulting in increases in grain yield	28
Camellia oleifera Abel	Streptomyces sp. 2GM57, *Amycolatopsis*	Shoot length and ground diameter significantly increased	29
Elaeis guineensis Jacq.	*Nocardiopsis sp.* ac9, *Streptomyces, Violaceorubidus* 6ca11, *Streptomyces* sp. ac19	Cellulase, Xylanase, Lignolytic activity	30
Setaria viridis var. pachystachys	*Streptomyces* sp. strain SANK 63997	Herbicidin H (herbicide)	31
Cucumis sativus	*Actinoplanes campanulatus, Micromonospora chalcea and Streptomyces spiralis*	Biocontrol against *Pythium aphanidermatum*	32
Eupatorium odoratum, Musa superb, Mirabilis jalapa, Curcuma longa, Clerodendrum colebrookianum, Alstonia scholaris, Centella asiatica,	*Leifsonia xyli* BPSAC24, *Streptomyces* sp. BPSAC34	Biocontrol against *Rhizoctonia solani, Fusarium graminearum, Fusarium oxysporum ciceri, Fusarium prolifratum, Fusarium oxysporum, Fusarium graminearum, Colletotrichum capsica*	33

Streptomyces niveus and *S. sanglieri* from leaves and roots of the tea plant, *Camellia* sp. and *Eurya japonica* showed positive plant growth-promoting characteristics such as phosphate solubilisation, IAA, ammonia, and siderophore production.

Saccharomonospora sp. and *Streptomyces yani* showed broad-spectrum antifungal activity. *Streptomyces* sp. has biosynthetic genes [i.e., Chitinase, Nonribosomal Peptide Synthetase (NRPS), and Polyketide Synthase (PKS)] that suggest their role in the inhibition of fungal phytopathogens.[23] Due to its antifungal activities, formulated actinobacteria spores can be utilised as biofungicides.[24] Some of the actinobacteria contributions to plant growth promotion have been listed in Table 1.

4. PLANT GROWTH PROMOTION MECHANISM EMPLOYED BY ENDOPHYTES

Although most of the molecular mechanisms underpinning endophytic interactions with plants are poorly understood, some of these have been scientifically proven advantageous and effective.[34] Based on the potential it can be of two types: rhizospheric-found in the rhizospheric zone of the plants, and endophytic-which colonises inside the tissues of plants. Although rhizospheric and endophytic plant growth-promoting microorganisms do not utilise identical mechanisms, it employs similar mechanisms in plant growth promotion. The advantage of endophytes is that, once they enter and colonize the internal plant tissue, they are not exposed to the quirk of changing soil conditions.[35,36] Endophytes employ phytohormones production, uptake of phytonutrients, mineral solubilisation, lowering stress responses, and protection from pathogenic attack Figure. 1 Their functions enhance biomass and yield productivity of important cash crops in agriculture.[37]

4.1 Direct Beneficial Mechanisms

Direct mechanisms directly enhance plant development. It occurs when endophytes i) produce auxin, IAA, (Indole Acetic Acid), cytokinin, and gibberellic acid ii) acquire resources from an environment containing nitrogen, phosphorus, and iron iii) produces ACC (1-aminocyclopropane-1-carboxylate) deaminase which lowers ethylene levels.[38]

4.1.1 Phytohormone Production

IAA, ethylene, gibberellins, cytokinin, and abscisic acid are the major phytohormones formed in plants, and regulate development under various stress conditions.[39,40] These phytohormones stimulate plant cell growth and division. The most active auxin is IAA which boosts the growth of root hairs and lateral roots, thus facilitating water-nutrient uptake, making them capable of coping with water deficits. Indirectly by influencing the IAA transport endophytic bacteria alter the homeostasis of auxin.[41]

Different signaling pathways are involved in producing IAA by endophytes thus changing the IAA levels in plants. Endophytic bacteria *Pantoea alhagi* isolated from leaves of *Alhagi sparsifolia* have shown improved drought tolerance.[42] Wheat plant inoculated with an IAA-producing fungal endophyte *Penicillium roqueforti Thom.* has obstructed the transfer of Zn, Cd, Ni, Cu, and Pb heavy metals.[43] Gibberellic acid is crucial in different processes notably in seed germination, flowering, and elongation of the stem. A gibberellin-producing seed-borne endophyte *Bacillus amyloliquefaciens* RWL-1

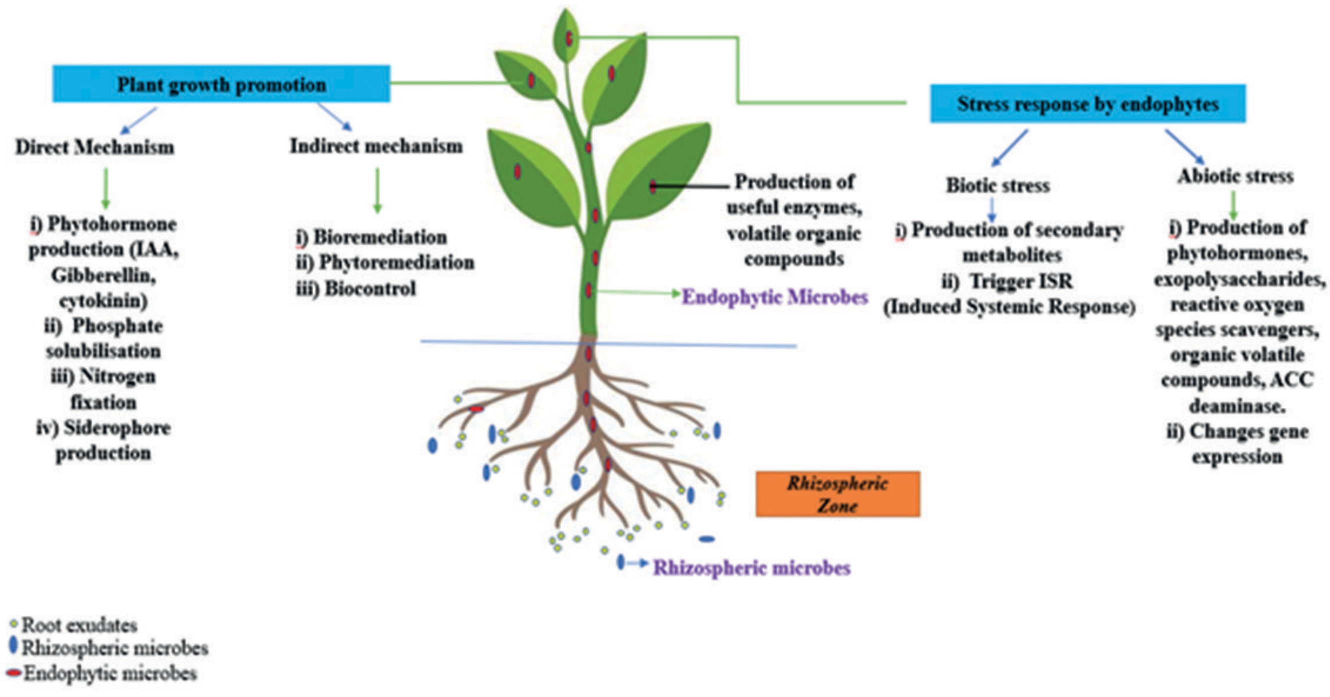

Figure 1. Role of endophytic microorganisms in plant growth, stress responses, and biological activities.

improves rice plant growth and induces regulation of endogenous phytohormones.[44] *Paenibacillus polymaxa* and *Pseudomonas resinovorans* from the leaves of *Gynura procumbens* have been found to produce cytokinin-like compounds helping in plant growth promotion.[45]

4.1.2 Nitrogen Fixation

Nitrogen limits the nutritional component in determining plant growth. This nutrient is primarily utilised by plants and made available through microbial nitrogen fixation done by mainly soil bacteria and archaea. It serves as a signaling molecule in most biochemical and physiological reactions. Nitrate and ammonia are preferred sources of nitrogen in plants. Nitrogen-fixing endophytes meet the nitrogen demands in the ecosystem. Biological N_2 fixation is needed to fulfill the demands of sustainable agriculture by decreasing the utilisation of synthetic-nitrogen fertilizers globally.[46,47] The ATP-dependent nitrogenase enzyme catalyzes the reduction of dinitrogen to ammonia. Nitrogenase is sensitive to oxygen. Some plant families involved in nitrogen-fixing, transfer microbes in lower oxygen modules-they fix nitrogen and deliver it to root tissues. Another plant family involves endophytic symbiosis consisting of microorganisms that inhabit the plant's internal tissues and go into the soil to extend themselves. Mycorrhizal and dark septate fungi are responsible for such nutritional symbiosis in numerous families of plants.[48] Endophytic diazotrophs such *as Paenibacillus polymyxa* strains P2b-2R can colonize hosts intracellularly to fix nitrogen, whereas in general, it takes several months to fix it.[49]

It has been found that endophytic diazotrophs *Lysinibacillus sphaericus* isolated from rice plants play an essential role in nitrogen fixation with biocontrol activity.[50] *Gluconacetobacter* and *Herbaspirillum* were isolated from the stem of sugarcane and identified as probable endophytic nitrogen-fixing bacteria.[51] Prokaryotic endophytes that establish symbiosis by their capability of fixing nitrogen have immense potential in sustainable agriculture. In recent decades, nitrogen-fixing free-living endophytic bacteria have become research subjects. Legume-Rhizobium symbiosis is still studied extensively towards enhancing Nitrogen – fixation efficacy through plant and bacterial genome manipulation.[52]

4.1.3 Phosphate Solubilisation

Next to nitrogen, phosphorus (PO_4) is the most growth-limiting macronutrient. As most phosphorus reserves are rock, which is insoluble, it causes a phosphorus deficiency in plants.[53] Phosphorus has functional and structural roles holding great significance. Structurally, PO_4 is the elementary unit for DNA (deoxyribonucleic acid), RNA (ribonucleic acid), and the lipid layer. PO_4 is utilised in the process of phosphorylation shows its significant importance in the formation of intermediates in different biochemical reactions such as Krebs's cycle and photosynthesis.[54] It is also an essential element of ATP for cellular energy. Endophytes can facilitate plant development by acquiring PO_4 or by increasing nutrient uptake, stimulating root growth and root hairs.[55-57]

Recent studies on bacterial endophytes from *Zea nicaraguensis* have shown that it colonises root hairs intracellularly in annual ryegrass (*Lolium multiflorum*), promoting solubilisation of insoluble phosphorus present in the rock. It also gave an interesting observation that endophytes host specific cells suggesting its target ability in only a critical cell type. Host recognition machinery is conserved for endophytes despite colonising in two divergent evolutionary hosts.[58] *Bacillus* and *Pseudomonas* are important bacterial genera, while *Aspergillus* and *Penicillium* form the important fungal genera of mineral phosphate solubilisers.[59]

4.1.4 Siderophore Production

Iron is an important element required in diverse metabolic cellular pathways. Hundreds of enzymes possess iron as a cofactor or heme groups.[60] To meet the requirements of iron, endophytes secret siderophore, a secondary metabolite. Siderophores are those molecules designed to produce strong and stable complexes with the cooperation of ferric ions. Four different moieties form four chemical classes of siderophore; catecholate, phenolate, hydroxamate, and carboxylate. When iron resources are clustered and bacterial cells are immobile, siderophores production is a more beneficial mechanism for the uptake of iron.[61] A study elucidated that siderophore production by bacterial species can suppress pathogenic microorganisms by taking away iron in a completion.[62] Gram-positive uptake of iron-loaded siderophore and gram-negative bacteria recognising siderophore through β barrel receptor in the outer membrane.[63] Bacterial siderophores exhibit a wide range of functional groups, whereas most fungi produce hydroxamate siderophores.[64]

Many bacterial and fungal endophytes are reported which along with phytohormone production and phosphate solubilisation, also synthesize siderophore to provide iron to plants. Endophytic bacteria improve the transportation of stored iron. Seed endophytes in wheat have been reported to enhance bioavailability and iron storage. These endophytes are involved in expressing metal tolerance protein (MTPs) phytases and ferritins.[65] Diazotrophic endophyte *Herbaspirillum seropedicae* induce gene transcripts for synthesis and translocation of phytosiderophores and PS-iron (phytosiderophore-iron) complexes.[66] *Streptomyces sporocinereus* OsiSh-2, an endophyte in rice plants, showed antagonistic activity against the rice blast-causing pathogenic microorganism *Magnaporthe oryzae*, due to iron competition.[67]

4.1.5 ACC Deaminase Production

The ethylene biosynthetic pathway contains a step in which S-adenosylmethionine (S-AdoMet) is converted into 1-aminocyclopropane-1 carboxylate (ACC), the immediate precursor of ethylene, by enzyme 1-aminocyclopropane-1-carboxylate synthase. Biosynthetic pathways regulation depends on abiotic and biotic stresses, which regulate plant activities[16]. Under stress conditions, root and shoot growth is severely affected because ethylene endogenously regulates plant homeostasis. ACC deaminase-producing endophytes degrade and confiscate plant ACC to supply energy and nitrogen. Endophytes take up ACC before its oxidation and improve plant strain by proficiently inhibiting ethylene formation.[68] By removing ACC, endophytes reduce the detrimental effects of ethylene, such as inhibition of nodulation, thus helping them to cope with plant stress and promoting plant growth.[69] In recent research, an ACC deaminase deficient strain of endophyte *Serratia grimesii* BXF1 was transformed by acd S gene, leading to overexpression of ACC deaminase resulting in amplified growth and nodulation in *R. tropici* CIAT 899, compared to the non-transformed strains.[70]

4.2 Indirect Beneficial Mechanisms

Endophytes alleviate stress through bioremediation, heavy metal detoxification, phytoaccumulation, phytoremediation, and by prompting complete resistance to plant pathogenic attack.

4.2.1 Bioremediation and Phytoremediation

Bioremediation is a low-cost, most advanced, and effective method of biotechnology that uses different organisms in the removal of contaminants and converts it into less polluting substances with less impact on humans and the environment.[71] In recent years, endophytes have become an emerging tool for the bioremediation of pollutants.[72] *Pseudomonas putida* has been found to improve the degradation of crude oil demonstrating its potential in bioremediation.[73] Chromium-resistant endophytes *Aspergillus fumigatus*, *Rhizopus* sp., *Penicillium radicum*, and *Fusarium proliferatum* biotransform it in the soil, promoting Cr-stressed *Lactuca sativa* to maintain its growth.[74] Mixed cultures of actinobacteria had successfully removed chlordane, a pesticide that had adverse effects on human welfare and the environment.[75]

Phytoremediation is an *in-situ* bioremediation technology for highly contaminated soils. Organic toxic contaminants are removed by various enzymes secreted by endophytes.[76] During the process of phytoremediation, endophytes help to decrease phytotoxicity and evapotranspiration of volatile contaminatants.[77] In a recent approach of clean-up through phytoremediation of Arsenic (As) by As tolerant endophytes isolated from *Lantana camara*, inhabiting the contaminated site, were successfully transferred within *Solanum nigram*. Besides increasing bioaccumulation of As, it improves plant growth when applied as a consortium under As stress.[78]

4.2.2 Production of Bioactive Compounds

There are largely hidden opportunities in the discovery of bioactive compounds with distinct chemical structures that evolved in plants. These molecules are crucial in communication between organisms, plant adaptation, and protection. Acting as natural antagonists, endophytes reduce plant-pathogen interactions by competing for the nutrient in an eco-friendly manner.[79] Endophyte produces chemical substances harmful to pathogens in the same ecological niche.[80] A novel bioactive compound harziaphilic acid was isolated from the co-culture of the biocontrol agent *Trichoderma harzianum* and endophyte *Talaromyces pinophilus* F36CF. *Eucryphia cordifolia* harbors an endophytic fungus, *Gliocladium sp.* discovered to produce volatile antimicrobial compounds. One such compound characterised as annulene, utilised as rocket fuel, brought to light for the first time, produced by endophytic fungus.[81] Fungal endophyte *Nodulisporium sp.* isolated from *Bontia daphnoides* has been identified as a producer of nodulisporic compounds. These are indole diterpenes that possess insecticidal properties against blowfly larvae.[82] Plants that belong to unique environmental settings exhibit unusual biology, that is endemic, and grow in areas of rich biodiversity, may harbor endophytes that produce novel and unique bioactive compounds to combat environmental stress.

4.2.3 Biocontrol

The Association of plants with microbes can be pathogenic, associative, symbiotic, or naturalistic and protect them from herbivores and insects. Several metabolites like flavones and flavonoids are produced in response to microbial adhesion to the root surface which also possesses antimicrobial properties, suggesting their role as a biocontrol agent. As a defense measure, it secretes a variety of signaling molecules.[83]

Endophytes can upregulate jasmonate pathways and salicylic acid (SA) and, ethylene thus reducing stress, disease severity, and protection from herbivores and insects.[84] The induced systemic response restricts pathogen entry and increased the expression of pathogen-related proteins and phenolic compounds.[85] Most endophytes, rhizospheric bacteria belonging to genera *Bacillus* and *Pseudomonas*, can be effective agents of biocontrol. A wide variety of lipopeptides produced by endophytes results in leakage in fungal hyphal membranes transforming them into inefficient and avirulent pathogens of plants thus inducing a ‘quorum-quenching effect.[86-87] Ambuic acid, produced from the endophytic fungus *Pestalotiopsis microspora* was active against several *Fusarium* and *Pythium* species[88]. Fungal endophytes of *Populus alba L*, confer resistance to trees from *Venturia tremulae Aderh*., which causes dieback in trees.[89] *Pseudomonas putida* PICP2 and *P. fluorescens* PICF7 are environment-friendly.[90] Lime leaves showed complete control against citrus canker.[91] *Curtobacterium*, an endophytic bacteria found in maize, soybean, strawberry, and grapevine can act by stimulating plant resistance and phytoremediation.[92]

Further studies in conferring resistance to cacao plant by endophytes showed an increase in phytoalexins such as cyclohexene, 2 methoxy-guaiacol, and 2, 3, -dihydrobenzofuran.[93] Another remarkable finding suggests that horizontal gene transfer of resistant genes from endophytic fungi might provide resistance to phytopathogens.

Flat gene transfer of Fhb7 from endophyte *Epichloe* species to *Thinopyrum elongatum*, confers resistance against *Fusarium*. Fhb7 detoxifies trichothecenes via de-epoxidation and its introgressions in wheat provide confrontation to fusarium head blight and crown rot.[94]

4.2.4 Plant Stress Tolerance

Endophytes are extensively studied for their involvement in various stresses. Extreme heat, solar UV radiation (280-315nm), metal pollution, and frequent droughts drastically affect plants.[95] Abiotic stresses trigger the formation of hydroxyl radicals, superoxides, and hydrogen peroxides belonging to reactive oxygen species and significantly cause oxidative destruction to plant cell membranes, proteins, and nucleic acid. The q-PCR finding shows that the initial steps of bacterial colonisation triggered the upregulation of glutathione reductase and superoxide dismutase gene. This may reduce the destruction caused by oxidative stress in plants induced by pathogen ROS production.

Endophytes have the potential to reduce stress by altering the metabolism of plants. Endophytes induce cold resistance and produce related compounds to combat the adversity (like starch, proline, and phenolics) caused inside the plant.[96] Several other mechanisms include alteration in phytohormonal activity, production of volatile compounds, secondary metabolites, antioxidants, enhancing ACC deaminase activity, and production of osmolytes. It causes alteration in root stress morphology and helps the plant to adapt to various stress conditions.[97] The production of exopolysaccharides plays a vital function in water stress conditions or excessive salt concentrations in soil.[98-99]

Endophytic fungus *Epichloe coenophiala* residing *in Festuca arundinacea* (Tall fescue grass) was found to have a higher amount of osmoprotective mannitol and some antioxidant conferring resistance to plants under oxidative stress.[100] *Piriformospora indica* a fungus, induces stress in many plants.[101] The upregulation of drought defensive genes DREB2A, CBL1, RD29A, and ANAC072 is induced due to endophyte in Chinese cabbage treated with polyethylene glycol.[102]

5. CO-CULTURE OF ENDOPHYTIC MICROBES FOR THE PRODUCTION OF NOVEL BIOACTIVE COMPOUNDS AND EPIGENETIC MODIFIERS

Genomic sequencing of some endophytic fungi revealed that these organisms have certain secondary metabolites encoding gene clusters, some of which fail to express themselves under standard laboratory conditions. Some novel bioactive compounds can be isolated by co-culturing two or more endophytes where they trigger the silent gene clusters or by using specific elicitors. The growth of various fungi can be co-cultured with other endophytic organisms.[103] Two endophytic strains *Talaromyces purpureogenus* H4 and *Phanerochaete sp.* H2, isolated from *Handroanthus impetiginosus* leaves were able to produce meroterpenoid austin displaying trypanocidal activity.[104]

Some researchers have shown that the presence of endophytes reduces plant death to a great extent from pathogen attacks. Hydroxyl oxylipins are produced by the genes pvlox1 and pvlox2 of fungal endophyte *Paraconiothyrium* variable having lipoxygenase activity. The heterologous expression of the pvlox2 gene produces the PVLOX2 enzyme responsible for the production of 13 HPODE (13-hydroperoxy 9,-11-octadecadienoic acid). Upon interaction in dual culture with *Fusarium oxysporum*, pvlox2 levels were upregulated and none of the *F. oxysporum* genes varied. The induced expression of the beauvericin synthase gene in *F. oxysporum* leads to an increase in beauvericin level which inhibits *P. variable* growth. *P. variable* biotransforms this mycotoxin and decreases the amount in the interaction zone. It allows the expansion of endophytes in plants. Further planta interaction studies on *Arabidopsis thaliana* show that the *P. variable* has reduced the death caused by *F. oxysporum* to 85 per cent when present before the pathogen attack.[105]

Epigenetic modifiers are small molecule elicitors that encourage the synthesis of particular specialised metabolites. These elicitors cause a change in the proteins that package DNA into nucleosomes, forming chromatin structures. Histone acetylation and DNA methylation are two mechanisms by which epigenetic modifications are controlled. The processes involved in DNA methylation, posttranslational modification of histones, and non-coding RNAs have a significant role in the physiology and maintenance of homeostasis in plants, animals, and microorganisms.[106]

The formation of inappropriate quantities of compounds, and reduced ability or attenuation of endophytes to manufacture the compound is a significant challenge when grown in lab culture. This drives the findings of small chemical elicitors which stimulate epigenetic modifications in endophytes to actively induce the expression of silent gene clusters.[107] The biosynthetic gene cluster of fungi is often placed in the distal region of chromosomes where these epigenetic changes regulate genes. Small molecule inhibitors of histone deacetylase (HDAC) and DNA methyltransferase (DNMT) are effective in the production of metabolites by fungi.[108,109] Some of the compounds induced by epigenetic modifiers involving the treatment of fungi have been listed in Table 2.

6. GENE EXPRESSION STUDIES IN PLANT GROWTH PROMOTION BY ENDOPHYTES

Gene expression studies are beneficial tools in the context of understanding and comparing the responses of an organism with its environment. Hybridisation-based microarray to RNA sequencing is a powerful approach to detecting the role of endophytes in inducing tolerance. A study with endophyte *Herbaspirillum seropedicae* revealed that 255 genes were differentially expressed, 59 of which were stress related. These genes were related to secondary metabolite production, hormone signaling, cell wall synthesis, proteolysis, PR proteins, and peroxidases.

Table 2. Compounds induced by epigenetic modifiers through treatment of fungi

Endophytes	Epigenetic modifiers	Mode of action	Induced compound	Reference
Penicillium concavoradulozum VE892	Quercetin	Inhibition of HDAC of classes III, Inhibition of protein kinases, inhibits DNA topoisomerases, and regulates gene expression	vinblastine	110
Lophiotrema sp. F6932, Muyocopron laterale F5912, and *Colletotrichum tropicicola F10154*	5-azacytidine and suberoylanilide hydroxamic acid (SAHA)	DNA methyltransferase Inhibition and deacetylases inhibitor	palmarumycin C8 and five novel compounds; palmarumycin CP30, muyocopronol A-C, and tropicicolide	111
Macrophomina phaseolina	sodium valproate	Histone acetylation	3-acetyl-3-methyl dihydro-furan-2(3H)-one (3) and methyl-2-(methyl-thio)-butyrate (4), plus volatile chemicals: butylated hydroxtoluene (BHT), di-methyl-formamide, 3-amino-1-propanol, and 1,4-benzenediol, 2-amino-1-(O-methoxyphenyl) propane.	112
Aspergillus fumigatus (GA-L7)	Valproic acid	Inhibition of HDAC of classes I and II	fumiquinazoline C	113
Co-culture of *Chaetomium sp.* and bacterium *Bacillus subtilis*	Suberoylanilide hydroxamic acid	Inhibition of HDAC of classes I and II	isosulochrin	114
Pestalotiopsis crassiuscula	5-azacytidine	Inhibition of DNA methyl transferase	4,6-dihydroxy- 7-hydroxymethyl-3-methoxymethylcoumarin	115
Penicillium herquei	5-aza-2- deoxycytidine	Inhibition of DNA methyl transferase.	α-pyrone derivatives	116
Co-culture of endophytic fungus *Phomopsis sp.* XP-8 and resveratrol-producing *Alternaria sp.* MG1 spores	Ethanol, sodium butyrate	Inhibition of HDAC of classes I and II	pinoresinol, pinoresinol monoglucoside, pinoresinol diglucoside	117
Dimorphosporicola tragani CF-090383	5-azacytidine and valproic acid, XAD-16 resin	Inhibition of DNA methyl transferase, Inhibition of HDAC of classes I and II, XAD-16 resin-unknown	Mycotoxin dendrodolides and fatty acid synthesis inhibitor, cerulenin (in presence of XAD-16 resin)	118

Gene transcripts help in cell wall synthesis, cell motility, and nitrogen fixation, and were mostly expressed in endophyte *H. seropedicae.*[66] High expression (upregulation) of spP5CS1 and spP5CS2 genes were recorded, which involved proline acquisition in sorghum leaves in drought.[119] Studies of gene expression were done to analyse the protective activity of endophyte *Serendipita vermifera* against *Bipolaris sorokiniana* infection in barley root tissue. The investigation leads to the finding that *S. vermifera* identifies modification done by the pathogen in the plant and resulted in the upregulation of detoxification and redox homeostasis-related genes. Genes that encode CAZymes (Carbohydrate-Active Enzymes) and presumed effectors were induced significantly, while genes encoding secreted proteins were found to be suppressed in *B. sorokiniana.*[120] Endophytic *Fusarium sp.* induces the gene involved in protein degradation by ubiquitin mediation.[121] For Cd and Ni stress, the most relevant genes, like OsGST and OsMPT1, were studied for gene expression in rice plants treated with endophytes. The OsGST expression was highly upregulated and lowered in treated inoculated plants.[122]

7. ROLE IN HERBICIDE RESISTANCE AND INSECT CONTROL

Xenobiotics and pesticide degradation by microorganisms is an adaptation that uses metabolic activities to survive in an adverse environment.[123] Microbial biotransformation of herbicides by oxidation, reduction, bond cleavage by lyases, and hydrolytic reactions has been described in many studies.[124-126] Endophyte *Pseudomonas putida* POPHV6, harboring inside the tissue of poplar, has been shown to cause the vanishing of 2,4-D from soil and decrease its translocation.[127] Endophytic bacteria also play role in the detoxification of glyphosate and s-triazine atrazine pesticides in soil application.[128,129] Endophytic bacteria *Burkholderia xenovorans* producing protein BphKLB400 imparts the potential to bioremediate several pesticides. BphKLB400 shows a similar sequence to glutathione transferases (GSTs) involved in xenobiotic compound detoxification and catalyze dechlorination reactions.[130] Microbial endophytes in many wild types of grass and weeds contribute to herbicide resistance which may cause a global problem.

Numerous research works elucidate the involvement of endophytes in insect control. Endophyte-colonised grasses show higher resistance to insects and produce biologically active alkaloids which interfere with the life cycle of insets. Endophytic fungus *Beauveria bassiana* has caused the death of mycoses insects in the banana plant when inoculated in rhizome.[131] Another finding suggested that the endophytic fungus *Chaetomium globosum* inhibited root-knot nematode.[132] Insecticidal activity has been reported against *Spodoptera littoralis*, a polyphagous insect by endophyte *Sarocladium strictum*, isolated from *Cyanchum acutum.*[133]

8. GENETICALLY MODIFIED ENDOPHYTES

Modifying the endophytic genome can be a more suitable strategy rather than manipulating the host plant genome.[134] In a recent study, it has been found that a genetically engineered strain of *Pseudomonas sp*. 102515, harboring an expression plasmid showed increased yield in the amount of a carotenoid, zeaxanthin diglucoside than its wild type.[135] To control insects, bacterial endophyte *Clavibacter xyli* was genetically modified to express endotoxin.[136] To protect against *Bombyx mori*, endophyte was genetically modified for biocontrol against *Fusarium,* and *Pseudomonas putida* to reduce the fungal population.[137]

9. LOSS OF ENDOPHYTIC SYMBIONTS

It has been found that symbiotic microbes may disappear in domestication and long-lasting cultivation. Using inorganic fertilisers, pesticides, and fungicides harms the endophytic population. In an investigation, seven years of continuous cultivation and seed cleansing of a wild variety of tobacco (*Nicotiana attenuata*) leads to the loss of symbiotic microbes and reduced resistance against the fungal pathogen of genera *Alternaria* and *Fusarium.*[138] The reintroduction of symbiotic microorganisms from the wild variety of tobacco confers resistance to some fungal diseases. Procuring symbiotic microbes from uncultivated plants in cotton helps the cotton seedlings to combat stress and diseases more effectively.[139] The increased level of diseases and pests may be because of the eradication of symbiotic microorganisms in cotton seeds. Cultivated crops such as maize have been intensely transformed, and many beneficial microbes have been lost. Modern hybrid maize needs more nitrogen and pesticide to enhance productivity than older Indian maize or tropical maize- causing loss of endophytes in hybrid maize.[140] One solution is the reacquisition of endophytic microorganisms from their wild-related crops into the cultivated crop as treatment of seed.

10. CONCLUSION AND FUTURE PERSPECTIVE

Abiotic environmental stress is a significant limitation for worldwide crop development and productivity. Global warming and water shortages negatively affect the current situation. Endophytes serve as potential candidates for a sustainable agriculture system. It is now well-established that almost every individual plant inhabiting this earth, almost every tissue of the plant, is colonised by one or several endophytes. The endophytes should have some characteristics to fulfill their requirement to exploit themselves in agricultural needs. They must not provoke plant diseases, should be culturable, and can colonize plants.

As stated in the review, endophytes have numerous roles in benefitting host plants that are impossible for a synthetic molecule to provide a wide range of positive functions. However, little effort must be done to increase the endophyte's efficiency for developing as a powerful tool in agriculture. The current efforts to find and implement endophytic microbes in plants are the beginning step to improving plant health, enhancing productivity, and decreasing chemicals in crop production. Thus, the alternative approach is to search for beneficial plant microbial symbionts that provide tolerance to significant environmental stress. Genetic manipulation in the endophyte's genome can be an alternative strategy to confer new desirable traits in it to improve plant growth promotion.

In the last 50 years, we have witnessed uncontrolled pesticides, herbicides, and chemical fertilizers in agricultural applications. We are not only introducing new selection pressure on weeds, pests, and pathogens but also on beneficial symbiotic microbes and endophytes. Many efforts must be done to the identification of more beneficial endophytes and cropping techniques that do not harm the diversity of endophytes. Identifying endophytes that can be used as bioinoculants, bio-fertilisers, and biopesticides with specific inoculum concentrations should be prioritised.

Along with chemical pesticides, formulations of sprayable endophytes can be developed for effective integrated pest management. Enhancement in industrial production by increasing the performance of culture bioreactors at the lab scale must be executed. Suitable candidate strains must be screened by in vitro and in vivo testing for biomass production and commercialisation as potential biocontrol agents. Advanced progress in 'omics' technology such as proteomics, genomics, and metabolic engineering must be used with full potential to unravel novel pathways and mechanisms behind the biosynthesis of bioactive compounds by different endophytes in plants. Also, efforts must be made in a proper way to manage crops that involve transgenic endophytes.

In the review, we highlighted functions of microbes that have profound applications in the biotechnological aspect of agri-businesses. Moving on with current leads available, future research must be concerned with the identification of suitable kinds of endophytes and addressing their potential in field evaluation to give new insights for sustainable agriculture.

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