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Endophytes - A Potential Source of Powerful Bioactive Compounds: A Review

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ABSTRACT
Endophytes are endosymbiotic group of microorganisms that colonize in plants and microbes. The study focuses on the pertinent application of Endophytes in agriculture, industry, environment and pharmaceutics. Endophytes are evolving as vital components of plant microbiomes. This review evaluates some of the beneficial properties of endophytes and its tremendous potential in various biotechnological applications. Endophytes produce a wide range of compounds that are beneficial not only for plant growth and development but also for environmental protection and sustainability. The enzymes and pigments produced by them are outstanding in the field bioindustries and food applications. In addition, they have a vital role in agriculture by enhancing soil fertility through, nutrient assimilation, iron availability, phosphate solubilization and nitrogen fixation. The pharmaceutical application of endophytes towards drug discovery is inevitable. The present communication identifies the effective functions of endophytic microbes in various sectors. We also propose that endophytic microbes may reduce the use of agrochemicals and enhance the synthesis of metabolites that are antimicrobial, antioxidant and antitumor. Understanding the endophytes as potential resources in discovering innovative compounds for further exploration.
***Keywords**: Endophytes, Nutrient Assimilation, Nitrogen Fixation, Agrochemicals, Metabolites.*

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INTRODUCTION
An endophyte is defined as an endosymbiont, usually a bacterium or fungus, that resides inside a plant for the majority of its life cycle and does not infect plants. German botanist Johann Heinrich Friedrich Link initially wrote about them in 1809. Initially regarded as fungal plant diseases, Béchamp, a French scientist, gave them the name "microzymas". De Bary (1866) literally originated the term "endophyte," which is derived from the Greek terms "endon," which means "within," and "phyton," which means "plant." Endophytic fungi may promote the growth of their host plant by producing phytohormones or by increasing the plant's resistance to various stresses, and they can produce pesticides to protect plants from herbivores [1,2]. Endophytes are thought to infect a plant's interior tissues without harming the plant or generating an outward infection; in fact, endophytes may even be beneficial to the plant [3]. An enormous variety of microorganisms known as endophytes can be found in plants. [4]. Endophytes which grow in the intercellular spaces of higher plants are known in terms of diversity and pharmaceutical potential. The biological variety of endophytes has become clearer as hundreds of genera and species can be isolated from one plant [5]. Endophytes are isolated from marine algae and seaweeds [6]. The different environmental conditions of the plants enable the difference in the number and types of internal microorganisms present in it [7]. Many researchers classify endophytes to the category of Plant Growth Promoting Rhizobacteria (PGPR), as endophytes represent most of the features exhibited by the rhizobacteria, even more than them [8].

BENEFITS OF ENDOPHYTES
Plant Growth and Development
Phytostimulation
Phytostimulation is assisted by the manufacture of phytohormones which enables the growth of plants. There are diverse phytohormones that regulate the growth of plants. Auxin, gibberellin, cytokinin are some

of the essential phytohormones that helps in achieving morphological modifications to the plants. The utmost studied mechanism of growth promotion is by lowering the ethylene (plants hormone) levels in plants by the enzyme 1-aminocyclopropane-1-carboxylate (ACC) deaminase. Ethylene is produced from the amino-acid methionine, which is primarily converted to S-adenosyl-methionine (AdoMet) with the help of the enzyme S-AdoMet synthase (ADS). AdoMet is converted to 5-methyl-thio-adenosine (MTA), by the enzyme 1- aminocyclopropane1-carboxylate synthase (ACC synthase or ACS). MTA is then transformed back to methionine via the Yang-cycle to 1-aminocyclopropane-1-carboxylic acid (ACC), the precursor of Ethylene. The conversion of AdoMet to ACC by ACS is the first committed and generally considered as the rate-limiting step in the biosynthesis of Ethylene [9]. Certain bacterial endophytes like Arthrobacter spp. and Bacillus spp. in pepper plants (*Capsicum annuum*) and others like *Pseudomonas putida* and *Rhodococcus* spp. in peas (*Pisum sativum*) are showed to release the enzyme ACC-deaminase [10,11]. Some endophytes like Acinetobacter spp., *Azospirillum* spp., Azotobacter spp., and Bacillus spp. supports the plants in synthesis and upregulation of certain phytohormones like cytokinin, indole-3-acetic acid, jasmonates, abscisic acid, gibberellins and some octadecanoids supports the overall growth of the plants, along with traits of boosted photosynthetic efficiency, opening and closing of stomata, osmotic adjustments as well as enhanced nutrient uptake [6,12].

Cold and Drought Stress Tolerance

It is thought that endophytes can sense physical changes in the environment and physiological changes in plants. They can also control the production of certain genes and phytohormones in plants to help them adjust to their new surroundings. Numerous studies have attempted to explain the modifications that occur in plants upon inoculation with specific endophytes; nonetheless, the precise mechanism underlying this adaptability remains elusive. Tomato plants inoculated with psychrotolerant endophytic bacteria *Pseudomonas vancouverensis* OB155 and *P. frederiksbergensis* OS261, which is supposedly the reason for their enhanced adaptation to cold (10-120C) were found to exhibit less membrane damage and increased antioxidant activity in comparison to the control plants [13]. In another study, a whole-transcriptome sequencing of *B*urkholderia *phytofirmans* PsJN colonizing potato (Solanum tuberosum **L.**) plants was used to investigate the gene activity in the plants and the response of the strain PsJN to plant stress. The transcriptome of PsJN colonizing *in-vitro* propagated potato plants exhibited an extensive range of functionalities associated with the genome of strain PsJN. Transcripts involved in transcriptional regulation, cellular homeostasis, and the detoxification of reactive oxygen species, indicating an oxidative stress response in PsJN, were up regulated as a response to drought stress in plants [14]. Since endophytic bacteria can affect how plants respond physiologically to challenges, it is concluded that they have the potential to be employed as defensive agents in agricultural systems in harsh climates [15].

Biocontrol of Plant Disease

Endophytes are proved to have potential benefits in the biocontrol of plant pathogens [16]. The biocontrol of phytopathogens by endophytes are done either by direct inhibition of pathogens or indirectly by strengthening the immune system of plants which prevent the colonization of pathogens. The synthesis of inhibitory allele substances, such as antibiotics, hydrogen cyanide (HCN), iron-chelating siderophores, and antifungal metabolites, is the primary process involved in the direct inhibition of infections. [17]. Endophytic bacteria are also able to produce resistance-conferring Volatile Organic Compounds (VOCs) [18]. In a study, maize plants inoculated with endophytic Enterobacter aerogenes which synthesize VOC 2,3-butanediol exhibited enhanced resistance against the northern corn leaf blight disease whose causative agent is the fungus *Setosphaeria turcica* [19]. Another example involves the synthesis of a new lipopeptide by the endophyte Pseudomonas poae strain RE_1-1-14, which was initially isolated from the roots of sugar beets. Poaeamide has a role in inhibiting *Rhizoctonia solani*, a fungal disease. [20]. Bacteria depend on quorum sensing (QS) to survive in complex ecological niches. It controls the physiological processes that bacteria go through, such as competence, acclimatization, biofilm formation, communication between cells, and reproduction. By weakening the auto-inducer signals of pathogens, certain endophytic bacteria suppress Quorum Sensing (QS) and regulate plant pathogens [21]. For example, some endophytic bacterial strains of Cannabis sativa L. quench the QS signals of the biosensor strain *Chromobacterium violaceum*, preventing it from communicating with other cells in the plant [22]. One of the endophytic bacteria's indirect bio-control strategies is the generation of plant resistance, which suppresses a wide range of phytopathogens [23]. Bacterial endophytes have been reported to prime plants for intense defensive responses on the attack of pathogen without causing any major negative impacts to plants [24]. This process is determined either by Jasmonic Acid (JA), Salicilyc acid (SA), Ethylene (ET) or a combination of these signaling pathways. The highly competitive colonizer of several crop endophytes, *Enterobacter radicincitans* DSM 16656, has been shown in a study by Brock et al. (2013) to be able to induce priming in Arabidopsis through JA/ET- and SA-dependent pathways [25]. According to a different study, the endofungal bacterium *R. radiobacter* F4 can invade plant roots without regard for specificity and can strengthen a plant's defenses against bacterial leaf pathogens like *Pseudomonas syringae* pv. tomato DC3000 and *Xanthomonas translucens* pv. translucens [26]. These illustrations add to the increasing body of research on tactics that increase plant immunity by utilizing bacterial endophytes.

AGRICULTURAL APPLICATION

Nutrient Assimilation

In biofertilization, plant growth is encouraged by the accessibility of nutrients. One of the most useful functions of endophytes is that of their promising role as alternatives to maximize biological nitrogen fixation by plants, as these microorganisms have the capacity to colonize inside the roots of plants and suffer less competition than the rhizosphere bacteria. It is obvious that no natural soil is a reservoir of all vital nutrients for plants. Usually, one or more of the nutritional components required for plant growth are not present in sufficient amounts. Increased amounts of limiting plant nutrients can be obtained by the host plants with the assistance of endophytic bacteria [27].

Nitrogen availability

Endophytes are able to fix the atmospheric nitrogen to plant-labile form, by expressing nitrogenase activity, and make them available to the plants [28]. All nitrogen fixing bacteria are supposed to have the enzyme nitrogenase, which is a highly conserved protein, chemically with abundant evidence signifying lateral gene transfer [29]. Researchers have found that, under controlled circumstances, nitrogen-fixing bacteria such as Azoarcus sp. BH72, *Azospirillum brasilense, Burkholderia spp., Gluconacetobacter diazotrophicus*, and *Herbaspirillum seropedicae* improve the biomass of the host plant through atmospheric nitrogen fixation [30]. Though the endophytes are not as efficient as nitrogen-fixing bacteria like Rhizobium in roots, certain strains like *Gluconacetobacter diazotrophicus*; a symbiont of sugarcane and pine plants, are found to perform exceptionally well in case of atmospheric nitrogen fixation [31].

Phosphorus availability

Phosphorous is extra vital micronutrient essential for the enzymatic reactions which are accountable for majority of the physiological processes in plants [32]. Even though they are present in ample quantities, most of the soil phosphorus is in the insoluble form, and hence they are unavailable for the consumption of plants for their growth and development. Moreover, more than 70% of the phosphorous supplied to the plants in the form of chemical fertilizers tend to form insoluble complexes in the soil, which eventually becomes a threat to the plants, soil as well as environment. The only sustainable method of bio-fortification of phosphorous in soil is by the use of phosphate metabolizing microorganisms. It is studied that certain endophytes can enhance the availability of phosphorous to plants by adopting various mechanisms like acidification, chelation, ion exchange, production of organic acids and by secreting acid phosphatase which can mineralize organic phosphorus [33,34]. Phosphate solubilization feature is commonly found in endophytic bacteria. It has been reported that between 59% and 100% of endophytic populations from legumes such as soybeans, cacti, strawberries, sunflowers, and other plants were phosphate mineral solubilizers [35,36,37, 38].

Iron availability

Iron is another vital element of life obligatory for the better growth, metabolism and development of plants. Iron is part of many proteins which helps in monitoring important physiological processes like transpiration, respiration and photosynthesis. Iron, generally exist in the environment as insoluble ferric (Fe^{3+}), as in oxides or phosphates, they cannot be directly up-taken and utilized by the plants. Endophytes are showed to produce siderophore, which is a low molecular weight iron binding/chelating compounds, which are created during low iron stress [39]. An endophytic Streptomyces sp. GMKU 3100 was identified from the roots of an Oryza sativa L. cv. KDML105 Thai jasmine rice plant, and it has been demonstrated to produce a significant amount of siderophores [40].

ENVIRONMENTAL APPLICATION

Bioremediation

Bioremediation is a method that uses microbial metabolism to help remove contaminants from an area. Bioremediation involves a number of methods and approaches, such as rhizoremediation, which is typically employed to eliminate hazardous waste from the biosphere, and phytoremediation, which is boosted by endophytic bacteria [41]. According to recent research, the cooperation between endophytes and plants can be extremely important for the breakdown of dangerous pollutants in the rhizosphere. It was discovered that a sizable percentage of bacterial strains isolated from grapevine (*Vitis vinifera* L.) plants were resistant to manganese, nickel, zinc, lead, and mercury [42]. From the tissues of *Alyssum serpyllifolium* growing in serpentine soils in northeastern Portugal, nickel-resistant endophytic bacteria were identified [43]. It is also mentioned that some endophytes may break down petroleum and its byproducts. Methylobacterium populum sp. nov. strain BJ001, which was isolated from poplar trees, is shown to be capable of breaking down energetic chemicals including hexahydro-1,3,5-trinitro-1,3,5-triazine (HMX), hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX), and 2,4,6-trinitrotoluene (TNT). In a different case, toluene was phytoremediated using the strain of *Burkholderia cepacia* L.S.2.4 bacteria that had undergone genetic alteration through the inclusion of a pTOM toluene-degradation plasmid of B. cepaciaG4, a naturally occurring endophyte of yellow lupine [44]. In addition to the bioremediation of volatile organic compounds, a great deal of study has been done on how vegetation composition affects greenhouse gas emissions. According to studies, the two main greenhouse gases are carbon monoxide (CO) and methane (CH4). Recent research has revealed that methane is converted to carbon dioxide by endophytic methanotrophic bacteria found in Sphagnum spp. (moss), such as Methylocella palustris and *Methylocapsa acidiphila*. Sphagnum plants use carbon dioxide for photosynthesis [45].

INDUSTRIAL APPLICATION

Pigment Production

It has been demonstrated that some endophytes aid in the synthesis of pigment. Quercetin, a glycoside that is orange in color, was isolated from Penicillium sp., an endophytic fungus that grows in Ginkgo biloba L. This was previously described as quercetin glycoside that was produced from the twigs of Ginkgo biloba L by an endophytic fungus strain called SX01, which was subsequently identified as *Penicillium purpurogenum*. The strain was able to produce abundant soluble red pigments that may be used as natural food coloring [46]. It was discovered that a different pigment that was separated from the endophytic fungus *Monodictys castaneae* inhibited some human pathogenic bacteria more effectively than streptomycin, including *Staphylococcus aureus, Klebsiella pneumonia, Salmonella typhi*, and *Vibrio cholera* [47].

Enzyme Production

It has also been demonstrated that the endophytic organisms generate a variety of potentially medicinally useful enzymes. The endophytic fungus Eurotium sp. was isolated from the rhizomes of Curcuma longa and is known to generate asparaginase, a significant anti-cancer enzyme [48]. L10Q37 and LQ2F02, two strains of the endophytic fungus *Huperzia serrata*, also showed anti-acetylcholinesterase activity [49]. Many enzymes of commercial importance are synthesized by several endophytes. The search for other potential metabolites produced from endophytes had led to the discovery of a few vital enzymes. Endophytic fungi like *Acremonium terricola*, Aspergillus japonicas, *Fusarium lateritium, Monodictys castaneae, Nigrospora sphaerica, Penicillium aurantiogriseum, Pestalotiopsis guepinii, Phoma tropica, Phomopsis archeri, Tetraploa aristata*, and *Xylaria* sp. and many other unidentified species in *Opuntia ficus-indica* Mill. have obvious their important input in production of promising potential distribution in biotechnological processes involving production of pectinases, cellulases, xylanases, and proteases [50]. Certain cell wall hydrolases produced by a variety of microorganisms' exhibit hyperparasitic activity which helps in attacking pathogens [51]. Another enzyme, chitinase synthesized by an endophytic bacterium *Serratia plymuthica* C48 inhibited spore germination and germ-tube elongation in *Botrytis cinerea*, a fungal pathogen infecting grape, commonly called as "botrytis bunch rot" [52]. For Serratia marcescens to function as an antagonist against the necrotic fungal pathogen *Sclerotium rolfsii*, it is thought that the ability to manufacture extracellular chitinases is essential [53].

PHARMACEUTICAL APPLICATION

Bioactive compounds and secondary metabolites

The extra-nutritional components known as "bioactive" or "biologically active" chemicals are found in trace amounts in lipid-rich diets and plant products. It is thought that endophytic fungi are a good source of novel bioactive substances [54]. On the other hand, secondary metabolites are substances that are not necessary for an organism to grow, but they are important for adaptive functioning and serve as signaling molecules or components of defense systems during ecological interactions and environmental stressors. The antibacterial, antifungal, antiparasitic, anticancer, and antiviral properties of steroids, alkaloids, phenols, isocoumarins, xanthones, quinones, and terpenoids—all of which are secondary metabolites of endophytic fungi—have been reported [55,56]. Novel, advantageous bioactive compounds with biological properties like antibacterial, antidiabetic, antifungal, anti-inflammatory, antiprotozoal, antituberculosis, insecticidal, immunomodulatory, antiviral, anticancer, and anthelmintic activity have been reported in a number of studies [57,58,59]. Bioactive substances are currently chosen over synthetic medications for a variety of ailments since they have minimal adverse effects. Endophytic fungus *Pestalotiopsis neglecta* BAB-5510, which lives in Himalayan cypress *Cupressus torulosa*, is thought to be a promising source of phenols, flavonoids, terpenoids, alkaloids, tannins, polysaccharides, and saponins [60]. On the other hand, a medicinal plant known as *Atractylodes lancea* can produce volatile oils such as b-caryophyllene, zingiberene, caryophyllene oxide, b-sesquiphellandrene, hinesol, b-eudesmol, and atractylone when exposed to Gilmanielila sp.AL12, an endophytic fungus [61]. Another bioactive substance that is abundant in red and chili peppers is capsaicin, which is employed as an anti-tumor agent and pain reliever for a variety of human malignancies. Capsaicin is produced by the endophytic fungus *Alternaria alternata*, which was isolated from *Capsicum annum* [62]. In addition, endophytic actinomycetes seem to be a viable alternative source of bioactive compounds that could be used for crop protection and medicinal production. Over 140 actinomycetes genera have been identified thus far. Significant antibacterial activity was demonstrated by *Streptomyces rochei* CH1, an endophytic actinomycete of Cinnamomum sp., against a range of test pathogens, including *Pseudomonas aeruginosa, Vibrio parahemolyticus,* and *Aeromonas caviae* [63]. Broad range antibiotic activity against Escherichia coli MTCC 739, P. aeruginosa MTCC 2453, *Micrococcus luteus* NCIM 2170, *Staphylococcus aureus* MTCC, and yeast pathogen *Candida albicans* MTCC 3017 were demonstrated by *Streptomyces cyaneofuscatus* (KY287599). Additionally, Streptomyces KX852460 exhibited anti-fungal action against the causative agent of tobacco leaf target spot disease, *Rhizoctonia solani* AG-3 KX852461 [64].

Source of Drugs against Various Diseases

Numerous bioactive substances and secondary metabolites can be found in endophytes. Novel secondary metabolites found in endophytic bacteria can be a rich source of pharmaceuticals with anti-inflammatory, antimicrobial, anticancer, antidiabetic, anti-insect, and immunosuppressive properties [65,66]. The endophytic diversity and potential for producing bioactive secondary metabolites of only a few plants have been studied. Finding new secondary metabolites and bioactive substances from various endophytic microbe species is a significant step in replacing many manufactured medications that have the potential to have negative side effects. Many bioactive substances that have been commercially produced by various endophytic fungi found in respective plants, including camptothecin, diosgenin, hypericin, paclitaxel, podophyllotoxin, and vinblastine, are significant for both agriculture and medicine [67,68]. The most significant businesses that are spearheading the creation of endophytes-based products are Adaptive Symbiotic Technologies (US), Agricon (New Zealand), GrassLans Technology Ltd. (New Zealand), Biotelliga Ltd. (New Zealand, Auckland), and Intrinsyx Bio (US) [69]. Different metabolite separation and medical applications would be made possible by the metabolic diversity and distinct secondary metabolite pathways seen in endophytic fungus [70].

CONCLUSION

Nowadays Since they are widely available, endophytic fungi are thought to be a possible source in the production of drugs and secondary metabolites. Microorganisms known as endophytes inhabit the epidermal and aerial parts of plants and are found in a vast array of chemical compounds. Endophytic microbes generate bioactive chemicals and secondary metabolites that are utilized to manage infections and a variety of human health issues. This review's extensive coverage of endophytes' applications across a number of industries motivates scientists to continue monitoring endophytes as potential solutions to a host of environmental and human health issues. Thus, we came to the conclusion that using microbial endophytes is simpler, safer, less expensive, and more efficient.

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