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Review Article

BIOACTIVE SECONDARY METABOLITES DERIVED FROM ENDOPHYTES: A REVIEW

SHOBHA SINGARAPALLE[1], M. ABDULLAH HARH[2], CHEEPURI GOWTHAM PHANINDRA[2], D. JAGADEESWARA REDDY[3], PATRICK FRANCIS KIMARIYO[4], MURALI KRISHNA KUMAR MUTHYALA[1]*

[1]Department of Pharmaceutical Chemistry, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India. [2]Department of Pharmacognosy, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India. [3]Department of Pharmaceutical Biotechnology, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India. [4]Dar es Salaam Institute of Technology, Science and Laboratory Technology Department, Dar es Salaam, Tanzania. *Corresponding author: Murali Krishna Kumar Muthyala; Email: dr.mmkkumar@andhrauniversity.edu.in

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ABSTRACT

Endophytes comprise diverse bacteria, fungi, and actinomycetes that reside harmlessly within plant tissues, fostering complex ecological interactions that significantly enhance plant growth, stress resilience, and disease resistance. Since their discovery in the early 19th century, endophytes have become essential for sustainable agriculture, environmental conservation, and advances in therapy. They generate bioactive secondary metabolites, such as paclitaxel (Taxol), camptothecin, podophyllotoxin, and vincristine, critically important in cancer treatment. The varied biosynthetic pathways for metabolites, such as terpenoids, polyketides, alkaloids, flavonoids, and phenylpropanoids emphasize the biochemical versatility of endophytes. Leveraging these bacteria biotechnologically offers a sustainable and scalable alternative to conventional plant-based extraction, addressing the growing global demand for medicinal compounds while minimizing ecological impact. This review presents a detailed analysis of endophyte classification, ecological roles, and industrial applications, highlighting their significant contributions to advanced pharmaceutical research, sustainable agriculture, and bioremediation. Expanding research on plant-endophyte relationships may result in discovering new bioactive compounds, advancing the convergence of microbiology, biotechnology, and environmental science.

Keywords: Bioactive compounds, Biopharmaceuticals, Biotechnology, Endophytes, Plant-microbe interactions, Secondary metabolites, Sustainable agriculture.

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AN OVERVIEW OF ENDOPHYTES AND THEIR IMPORTANCE

Endophytes are microorganisms that form symbiotic relationships with plants by residing inside their tissues [1]. Endophytes promote plant fitness by strengthening stress tolerance, modifying biomass, optimizing water, and resource usage. Endophytes are strongly associated with plant life [2]. In 1809, Johann Heinrich Friedrich Link, a German botanist, first described endophytes [3]. In 1886, German botanist Anton de Bary, regarded as the father of plant pathology, coined the word endophyte [4]. In 1888, Dutch scientist Martinus Willem Beijerinck isolated root nodule bacteria in pure culture from *Leguminosae* plant nodules and demonstrated that *Rhizobium leguminosarum* can fix atmospheric nitrogen. Simultaneously, Hermann Hellriegel and Hermann Wilfarth recorded the mineral nitrogen independence of *leguminous* plants and the significance of rhizobia in symbiotic nitrogen fixation [5]. In 1898, Vogl initially isolated and cultured asymptomatic endophytes from the seeds of *Lolium temulentum* [6].

TYPES OF ENDOPHYTES

Endophytic bacteria, fungi, and actinomycetes are the main types of microorganisms that live within the tissues of plants without harming them [7].

Fungal endophytes

These are the most widely studied endophytes [8]. Notable examples of endophytic fungi are *Ascomycota*, *Zygomycota*, and *Basidiomycota* [9]. Endophytic fungi can be classified into two main groups based on their life history and evolutionary relationships [10]. The first group consists of clavicular endophytes, which colonize certain grasses. The second group consists of non-clavicular endophytes found in asymptomatic tissues of non-vascular plants, such as conifers, ferns, and angiosperms [11]. Endophytic fungi are recognized for synthesizing diverse secondary metabolites with potent biological activities, including anti-inflammatory, antioxidant, antifibrotic, and antiviral properties [12]. Isopestacin, derived from the microspore of the fungal endophyte *Pestalotiopsis*, has significant antioxidant effects. Taxol (Paclitaxel), a powerful chemotherapy compound, is produced by the endophytic fungus *Taxomyces andreanae*, which resides within the tissues of its host plant, *Taxus brevifolia* [13] Podophyllotoxin is an additional instance of an anticancer compound obtained from the endophytic fungus *Alternaria tenuissima* isolated from the plant *Sinopodophyllum emodi* (Wall.) Ying [14].

Bacterial endophytes

These are a significant category of endophytes that reside in different plant tissues [15]. Endophytic bacteria may be found in different plant specie's roots, stems, leaves, and seeds. They include many species, including Gram-positive and Gram-negative bacteria, such as *Bacillus*, *Agrobacterium*, *Brevibacterium,* and *Pseudomonas*[16]. Liu *et al.* latest research found that wild rice has a wide range of endophytes, with *Proteobacteria*, *Bacteroidetes*, and *Firmicutes* being the most prevalent [17]. The variety of endophytic bacteria in plants is affected by host and environmental variables, such as plant development phases, geographical location, and climatic conditions [18].

Endophytic Actinomycetes

These are often obtained from various plants, especially those in tropical rainforests, such as mangrove trees and medicinal herbs [19]. Plant roots have a greater quantity and variety of these microorganisms than other tissues, which is an intriguing observation about their distribution inside plants [20]. This implies that endophytic actinomycetes may have a specific and specialized function inside the root system [21]. *Streptomyces* and *Micromonospora* are the primary genera known for their exceptional ability to produce antibiotics and generate other beneficial bioactive chemicals [22]. The *Streptomyces* NRRL 30562 strain has a notable capacity to synthesize munumbicin D, a molecule with promising antibacterial activities [23]. The example of *Streptomyces* spp. *MSU*-2110 contains a wide variety of bioactive chemicals generated by endophytic actinomycetes. *Streptomyces* spp. MSU-2110 acts as a reservoir of coronamycin, an additional compound with promising anti-malarial properties [24].

CLASSIFICATION OF ENDOPHYTES ACCORDING TO THEIR BEHAVIOR AND TYPES OF INTERACTION WITH PLANTS

Host-specific and generalist endophytes

Host-specific endophytes exhibit a level of specialization toward certain genotypes or species of the host, perhaps influenced by genetic variables, such as effectors that impact host colonization [25]. Nevertheless, studies have shown that endophytic fungi in tropical grasses tend to be primarily host generalists, spreading to many grass lineages and even to non-grass plants [26]. An analysis of pine endophytes using amplicon sequencing revealed that although this technique may rapidly detect patterns of host specificity, it may not provide an accurate measure of the level of specialization due to the random inclusion of organisms that are not unique to the host [27]. Studying the makeup and behavior of fungal secretomes as they interact with plants might provide insights into how they adapt to varied environments, with specific proteins possibly affecting their ability to target specific hosts [28]. Genetic, ecological, and evolutionary variables determine the relative abundance of host-specific and generalist endophytes [29].

Obligate and facultative endophytes

Obligate endophytes are symbiotic with plants and live entirely inside them, but facultative endophytes may exist both inside and outside plants and provide advantages, including pest control and growth stimulation [30]. The development of obligatory symbiosis most likely includes a facultative stage in which symbionts might exist independently while benefiting from partnerships [31]. Accumulation occurs in waste treatment systems that can survive with or without oxygen when exposed to large amounts of organic matter, which leads to instability. However, systems that can only survive without oxygen remain stable and show an improved breakdown of volatile fatty acids and methane production [32]. Facultative endophytes give flexibility and diversity, while obligatory endophytes provide particular and constant plant advantages [33].

Mutualistic and non-mutualistic endophytes

Mutualistic endophytes form symbiotic relationships with host plants, providing advantages, such as stress tolerance, growth stimulation, and disease resistance [34]. They create bioactive compounds that help hosts adjust to environmental stressors [35]. Non-mutualistic endophytes, on the other hand, may contain mycoparasites that colonize both live plants and fungi, possibly expanding the metabolic gene repertoire for dual colonization [36]. These non-mutualistic endophytes may influence microbial populations in the rhizosphere, stimulate plant development, and change root exudation patterns [37]. Overall, mutualistic endophytes play an essential role in increasing plant health and resilience, although non-mutualistic endophytes may have a dual lifestyle of mycotrophy and mycoparasitism, exhibiting a wide range of ecological interactions within the microbiome [38].

IMPORTANCE OF ENDOPHYTES

The significance of endophytes in plants has been shown in Fig. 1 is as follows:

- Symbiotic relationships: Endophytes often form mutually beneficial relationships with their host plants, enhancing growth and health.
- Plant protection: Many endophytes produce bioactive compounds that protect plants from pathogens, pests, and herbivores.
- Stress tolerance: Some endophytes help plants tolerate environmental stresses, such as drought, salinity, and extreme temperatures.
- Nutrient acquisition: Certain endophytes assist plants in acquiring nutrients from the soil, particularly nitrogen and phosphorus.
- Phytohormone production: Endophytes produce plant growth hormones that stimulate plant development and improve overall health.
- Biodiversity: Endophytes contribute to the microbial diversity within ecosystems and play a role in maintaining ecological balance.

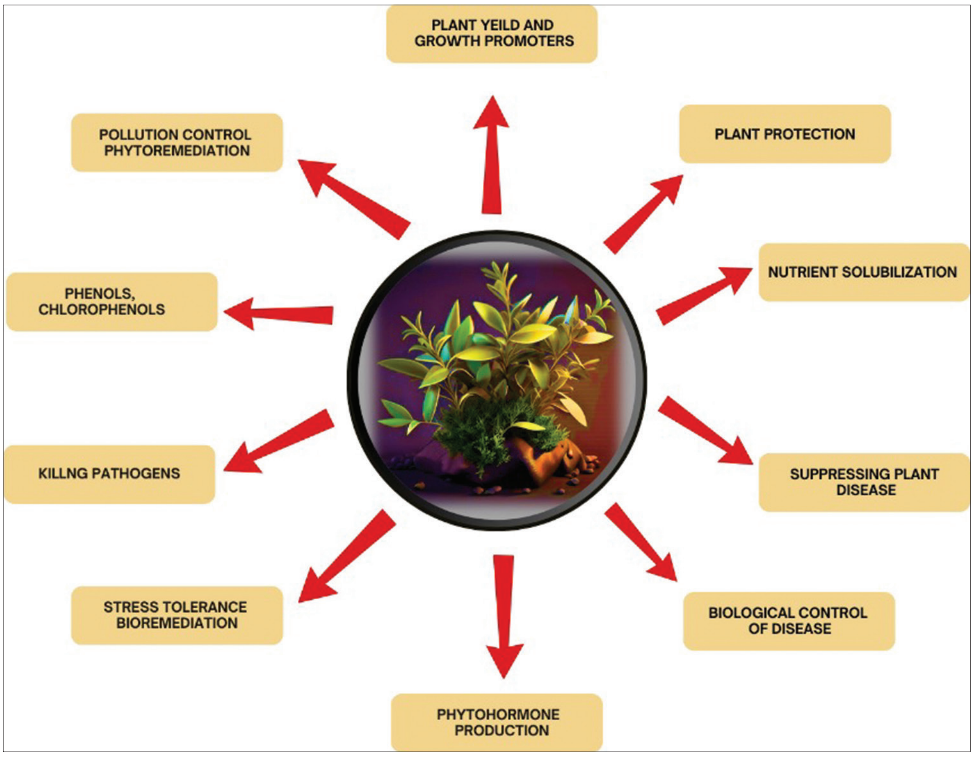

Fig. 1: Importance of endophytes in plants

- Biotechnological applications: Endophytes are sources of novel bioactive compounds with potential applications in medicine, agriculture, and industry.
- Bioremediation: Some endophytes can help plants degrade or accumulate environmental pollutants, aiding soil and water remediation.
- Crop improvement: Understanding and harnessing endophyte-plant interactions can lead to more resilient and productive crop varieties.
- Climate change mitigation: Endophytes may help plants adapt to changing environmental conditions and mitigate the effects of climate change on plant communities.

SYMBIOTIC INTERACTION BETWEEN ENDOPHYTES AND PLANTS

According to previous research, plants support diverse microbial communities that play critical roles in plant health, nutrient cycling, and ecosystem functions, as demonstrated in Fig. 2. Environmental conditions, plant species, and microbial diversity all influence these interactions. There are various habitats that plants provide for microorganisms [39].

External surfaces

Phyllosphere microbes on plant surfaces help nutrient cycling, disease management, and stress tolerance [40]. These bacteria recycle nitrogen, phosphorous, and potassium from organic materials to plants [41]. Beneficial bacteria occupy niches, produce antimicrobial chemicals, and stimulate the immune system of plants to fight infections [42]. Microbes produce stress hormones and improve nutrient and water absorption to help plants cope with abiotic challenges, including drought, salt, and severe temperatures [43].

Internal tissues

Microorganisms can invade and create endophytic populations throughout the plant. Endophytes have been found to help plants by enhancing nutrient absorption, stress tolerance, and disease defense [44].

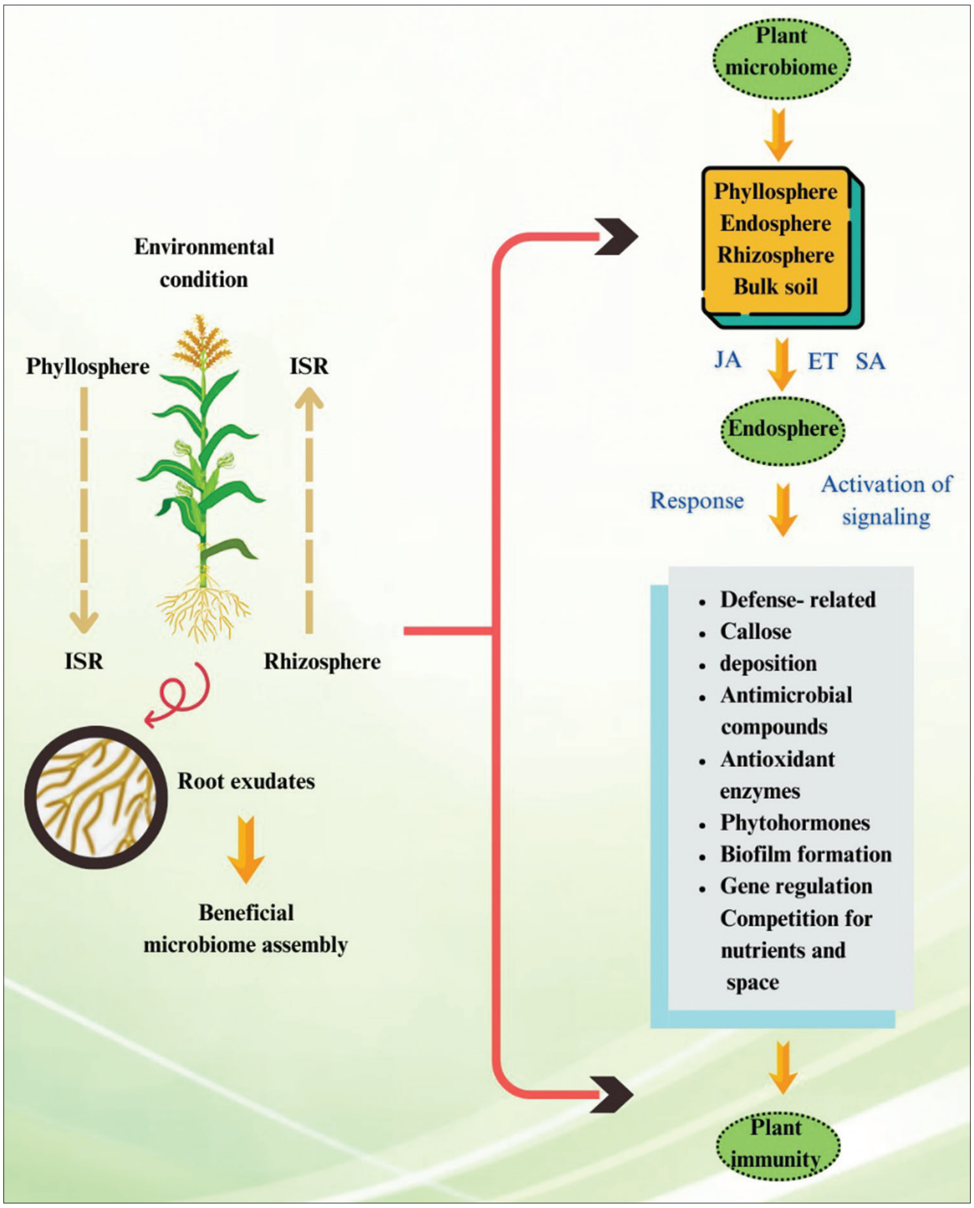

Fig. 2: Depicts how plant microbiomes boost immunity by activating systemic resistance and communication pathways. Root exudates assist beneficial microorganisms proliferating around roots, triggering defense mechanisms through jasmonic acid, ethylene, and salicylic acid signals. These create compounds that fight infections, influence gene activity, and compete for resources, improving plant health and defense

Rhizosphere
The rhizosphere, or soil area affected by plant roots, is a hotspot for microbial activity. Root exudates, or substances secreted by plant roots, attract and support various microbial populations [45]. Nutrient cycling, soil aggregation, and plant growth promotion rely heavily on the rhizosphere microbes [46].

Phyllosphere
The phyllosphere, which includes above-ground sections of plants, has a distinct microbial population that is regulated by leaf form, surface chemistry, and climatic conditions [47]. Microbes in the phyllosphere have been shown to affect plant health, disease resistance, and nutrient cycling [48]. Understanding phyllosphere microbiota is critical for managing plant diseases and improving agricultural methods [40].

Nectar and pollen
Flowers provide nectar and pollen as a reward for pollinators, which create new homes for microorganisms [49]. Microbial populations linked with nectar and pollen have been found, including yeast and bacteria. These bacteria may have an impact on pollination dynamics [50].

ENDOPHYTE INTERACTIONS IMPROVE PLANT GROWTH AND STRESS RESISTANCE

Plant endophytes promote pathogen competition, plant resistance, bioactive metabolite synthesis, and plant growth promotion to avoid disease [51]. Microbial formulations against phytopathogens employ endophytic *Bacillus, Burkholderia, Enterobacter, Pseudomonas,* and *Streptomyces* [52]. These metabolites include antibiotics, insecticides, antioxidants, anticancer, and antidiabetic [53].

Enhancing plant health: the function of arbuscular mycorrhizal fungi (AMF)
AMF establish mutually beneficial associations with the majority of land-dwelling plants, therefore improving plant well-being, nutrient absorption, resilience to stress, and ability to remove pollutants from the environment. AMF aid plants uptake of essential nutrients, such as phosphorus and nitrogen. This mutualistic relationship is facilitated by specialized structures called arbuscules, where fungi receive plant nutrients in exchange for strigolactones (SLs) that stimulate hyphal growth, thereby enhancing nutrient absorption. Some structures of strigolactones are illustrated in Fig. 3.

Plant adaptation and vitality
AMF bolster plants' capacity to withstand nutritional deficiencies in soils by enhancing nutrient accessibility and providing defense against diseases, drought, and salt. Plants without AMF have difficulties acquiring vital nutrients, resulting in stunted development and heightened susceptibility.

The function of phytohormones
Phytohormones, such as jasmonic acid and ethylene control plant growth, development, and defense mechanisms and influence symbiotic relationships with AMF. These hormones impact fungi colonization and the growth of symbiotic structures, maintaining a balance between defense and symbiosis.

Phytoremediation
AMF, in conjunction with specific bacteria and fungi, synthesizes substances, such as ferrochrome and fusarinines that form complexes with heavy metals, therefore increasing their accessibility for absorption by plants. This facilitates phytoremediation, enabling plants to purify polluted habitats, as shown in Fig. 4.

COMMUNICATION PROCESSES BETWEEN ENDOPHYTES AND PLANTS

Various activities by endophytic fungus and bacteria help plants grow and respond to stress. These bacteria generate phytohormones (auxin, cytokinin) and secondary metabolites that regulate plant development and stress tolerance [54]. RNA interference (RNAi) is crucial to bidirectional communication between plants and pathogenic fungi, and non-pathogenic endophytes may follow suit [55]. Favorable fungal endophytes that are restricted to the roots might produce systemic RNAi responses in host plants, modifying gene expression during mutualism and perhaps improving outcomes, as shown in Fig. 5. The intricate communication systems between endophytic microorganisms and plants are essential for plant health, stress tolerance, and growth [56].

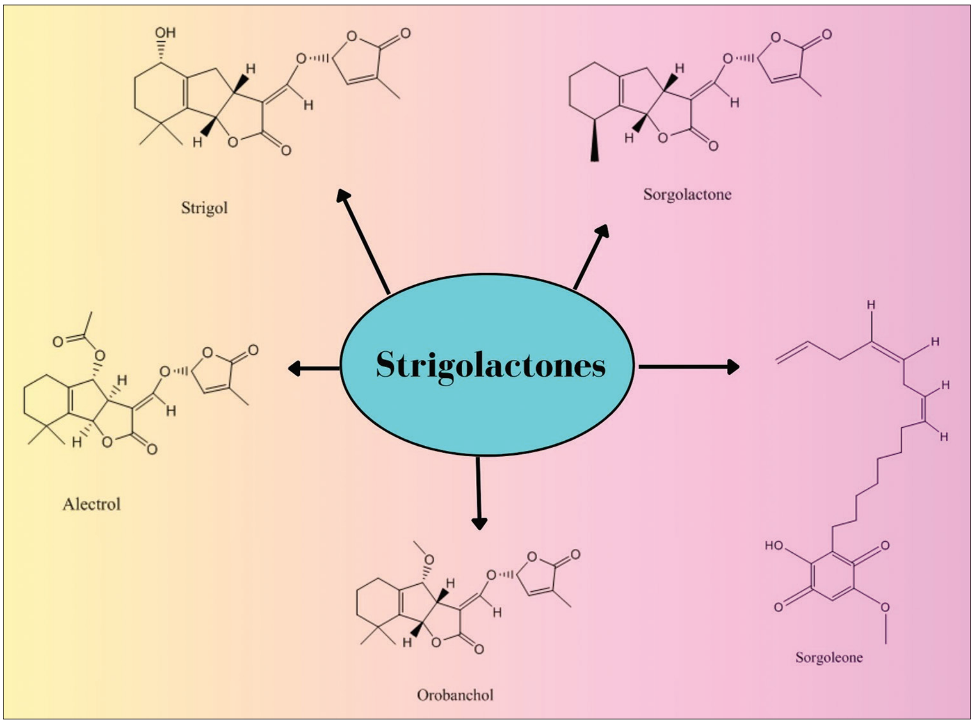

Fig. 3: Examples of strigolactones

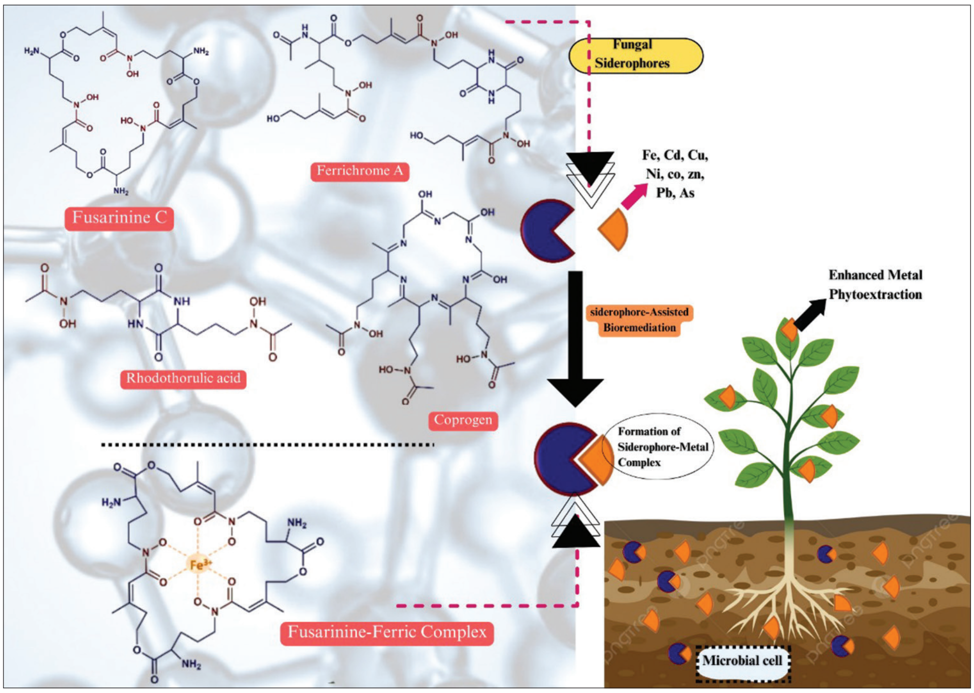

Fig. 4: Mutualistic interactions between plants and arbuscular mycorrhizal fungus (AMF), phytohormones in plant-fungal symbiosis, and phytoremediation

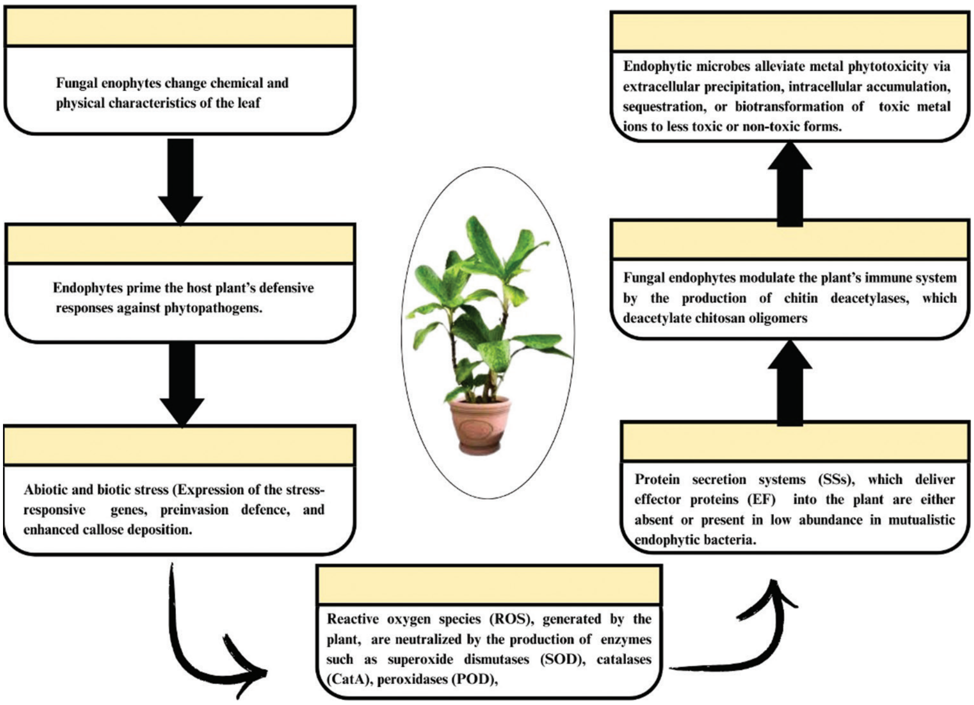

Fig. 5: Role of fungal endophytes in improving plant defence, stress tolerance, and herbivore deterrence

ROLE OF ENDOPHYTES AND THEIR METABOLITES IN PLANT DISEASE CONTROL

Endophytes and their metabolites enhance plant disease control by bolstering stress resilience and serving as biological agents [57]. They combat infections by niche competition, using antimicrobial chemicals, utilizing lytic enzymes, establishing systemic resistance, and generating hormones [58]. Induced systemic resistance (ISR) is facilitated by the signaling of jasmonic acid and ethylene, while systemic acquired resistance (SAR) depends on salicylic acid[59]. Endophytes may trigger ISR by the use of salicylic acid, indicating a potential connection between ISR and SAR [60]. Additional defensive mechanisms include the utilization of methyl jasmonate (MeJA) and brassinosteroids [61]. Roots secrete compounds, such as coumarins, that influence the microorganisms in the soil around the roots, referred to as the rhizosphere microbiota [59]. The essential elements are the Brutus protein (BTS), hormone receptors (HRs), microbe-associated molecular patterns (MAMPs), and pathogen-associated molecular patterns [62] are shown in Figs. 6 and 7.

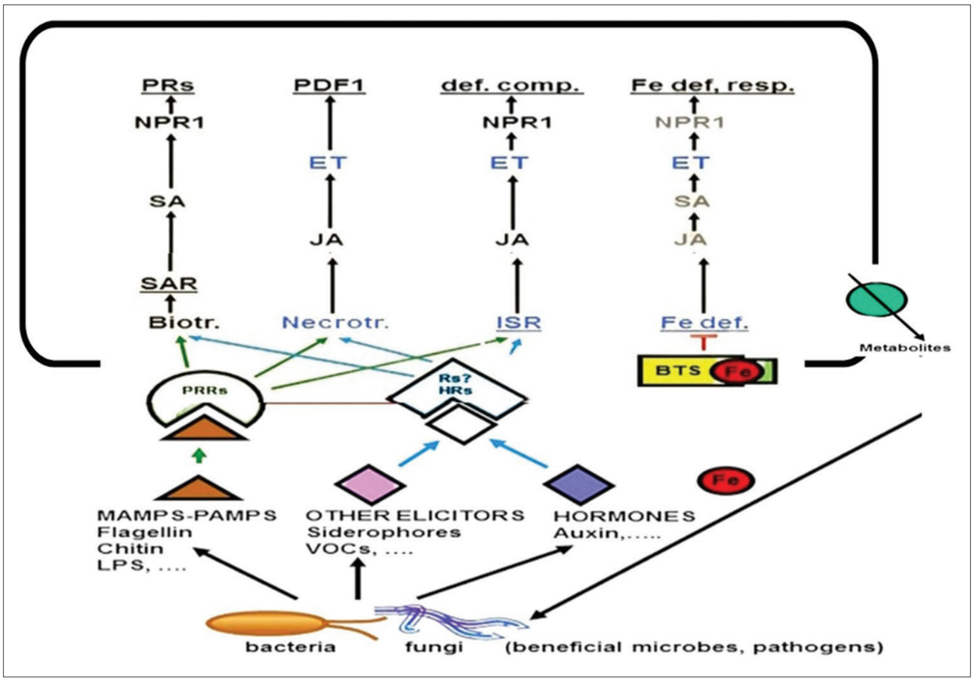

Fig.6: Interactions between the responses to iron shortage and the signaling of pathogens/bacteria in plants

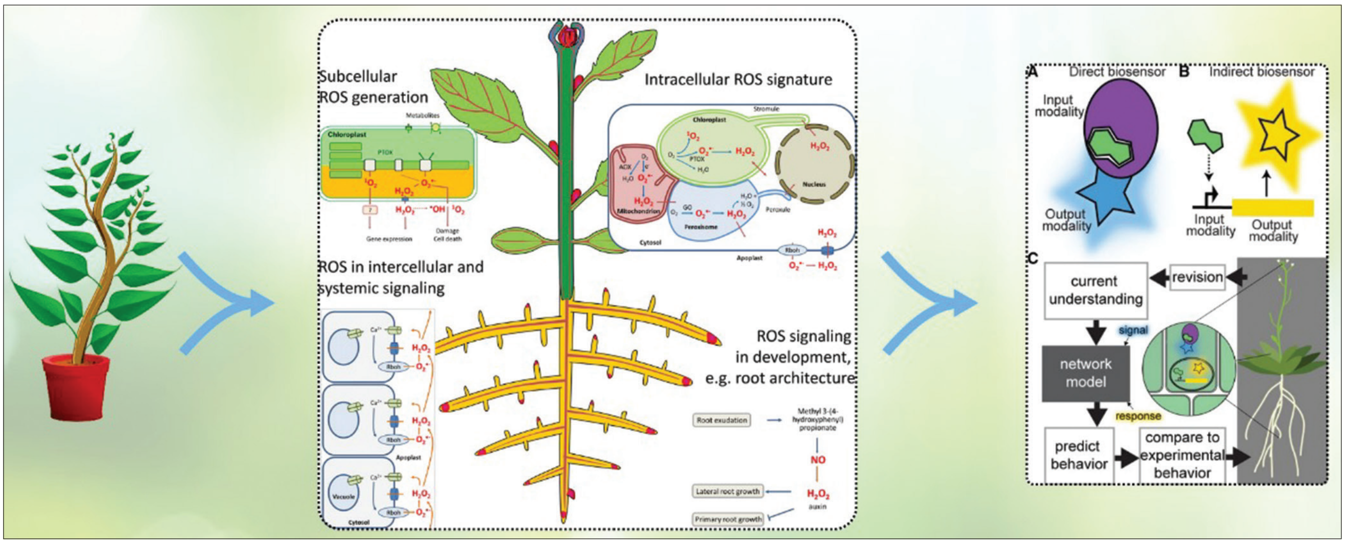

Fig. 7: The interactions between plants and endophytes lead to synthesizing secondary metabolites and the induction of plant defense systems

To promote plant growth

The endophytic bacteria *Rhizobium* spp., found in legumes that produce nodules, fixes atmospheric nitrogen, and improves plant growth and nitrogen availability. Biological control agents, such as *Trichoderma* spp., and endophytic fungi, produce antifungal compounds that protect the host plant from soil-borne illnesses, such as *Fusarium* [63]. For example, *Azospirillum brasilense*, a nitrogen-fixing endophytic bacterium, stimulates plant growth and nitrogen absorption through biological nitrogen fixation in crops, such as maize and wheat [64].

Tolerance to abiotic stress

Endophytic bacteria, such as *Bacillus* spp. generate osmoprotectants and antioxidants, which boost plant tolerance to drought and
AQ2 salt stress in crops, such as rice and soybean. One example for bioremediation. *Pseudomonas fluorescens*, an endophytic bacterium, can elicit systemic resistance in plants, enhancing their defense mechanisms against diseases, such as *Phytophthora* infestans in potato crops [65,66]. Furthermore, endophytic bacteria, such as *Methylobacterium* spp. produce auxins and cytokinins that facilitate the growth and development of crops, including tomatoes and cucumbers [67].

Improved plant productivity

Serendipita indica, an endophytic fungus, enhances nutrient absorption and stress tolerance in crops, such as barley and maize, leading to increased yields and enhanced agricultural production [68].

ROLE OF SECONDARY METABOLITES PRODUCED BY ENDOPHYTES IN PLANT BIOCHEMISTRY

Recognition

Endophytes release MAMPs, including flagellin and chitin, as well as damage-associated molecular patterns (DAMPs), which stimulate pattern recognition receptors on plant cells [69].

Signal transmission

when MAMPS (Microbe-Associated Molecular Patterns) or DAMPS (Damage-Associated Molecular Patterns) activate pathways, they transmit signals through phytohormones such as jasmonic acid, salicylic acid, ethylene, and calcium fluxes. These signals play a crucial role in regulating plant defence mechanisms, stress responses, and immune reactions against pathogens. Transcription factors (TFs) are either activated or inhibited by pathways that regulate the expression of genes responsible for secondary metabolite synthesis [69].

Gene activation

Occurs when TFs are activated and bind to DNA, initiating gene transcription and the production of enzymes necessary for metabolite synthesis [70].

Metabolite production

Enzymes play a vital role in catalyzing the production of alkaloids, phenolics, and other chemicals essential for defense and ecological functions. Reactive oxygen species and nitric oxide operate as signaling molecules, coordinating responses to endophyte infection. Strict control and communication across routes (such as jasmonic and salicylic acid) provide effective defense and flexibility [71].

Implications

Understanding this information results in enhanced plant resilience and the implementation of eco-friendly farming practices, ultimately leading to more significant crop conservation and yield [72].

ENDOPHYTES IN THE SYNTHESIS OF SECONDARY METABOLITES

Endophytes produce secondary metabolites that significantly contribute to the improvement of plant growth and development. The bioactive chemicals in plants play a crucial role in protecting the plant from viruses and pests, helping the plant withstand stress and absorb nutrients. The relationship between endophytes and host plants initiates a series of biochemical processes, including the stimulation of TFs that control the production of secondary metabolic pathways, as depicted in Fig. 8 [73].

IMPACT OF ENDOPHYTES ON THE FORMATION OF SECONDARY METABOLITES

Terpenoid biosynthesis

Taxol, a valuable anticancer drug, is produced by endophytic fungi of the *Taxomyces* species through terpenoid biosynthesis shown in Fig. 9. *Taxemes* fungi have been previously observed in *Taxus* spp. Plants that produce Taxol [74].

Limonin, a triterpenoid with anticancer and antiviral properties, is present in some endophytic fungi. Its biosynthesis is associated with terpenoid pathways, and fungal cultures can realize sustainable production [75]. Structures of both the limonin and paclitaxel are shown in Fig. 10.

Paclitaxel, originally from the *Taxus* tree, can be produced by endophytic fungi, offering a sustainable alternative. Its biosynthesis starts in the terpenoid pathway, where geranylgeranyl diphosphate (GGPP)

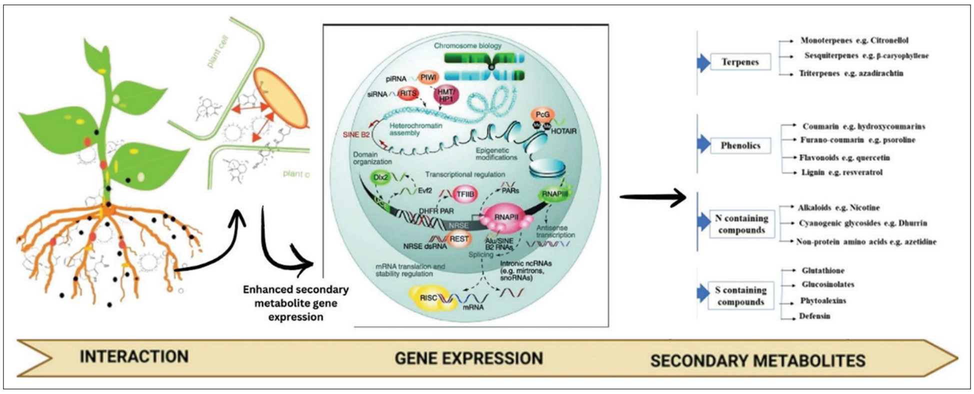

Fig. 8: Boosting plant health using endophyte-produced secondary metabolites

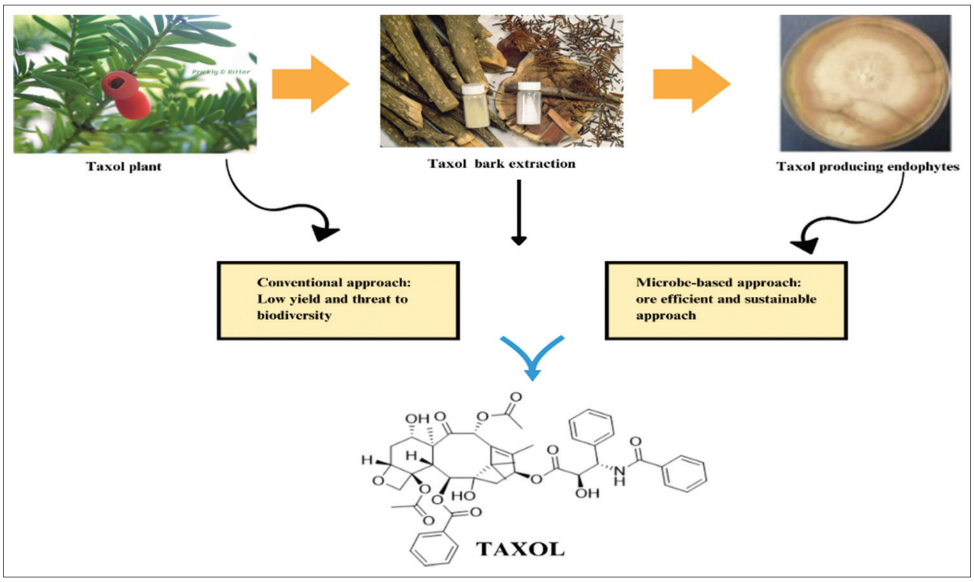

Fig. 9: Taxol production

is cyclized into taxadiene, which is then hydroxylated and modified to form paclitaxel. Endophytes, such as *T. andreanae*, sourced from *T. brevifolia*, and *Penicillium species* from *Taxus baccata*, mimic plant biochemical processes by incorporating genes from their host plants to produce paclitaxel independently [76]. This method mirrors plant processes and supports eco-friendly drug production [77].

Polyketide biosynthesis

Endophytic bacteria of *Streptomyces* species obtained from Pine trees have been shown to produce antibacterial polyketides. These compounds are produced by polyketide synthases and contribute to the host plant's defense against infections [78]. Aculeolamides, salaceyins, and Sespenines, bioactive compounds with antimicrobial and anticancer potential are produced by endophytic fungi. These metabolites are synthesized through polyketide or non-ribosomal peptide pathways, commonly found in fungi, such as *Penicillium* and *Aspergillus*. Endophytes live symbiotically within plants, utilizing metabolic pre-cursors and environmental cues to facilitate aculeolamides production. Cultivating these fungi in lab conditions offers a sustainable alternative for optimizing production, replacing traditional chemical synthesis and plant extraction methods [79]. Aureothin, a bioactive compound with antimicrobial and anticancer properties, is produced by endophytic fungi through the polyketide pathway. It exhibits potent anti-inflammatory and cytotoxic activities and can be sustainably produced by culturing these fungi in lab conditions [78].

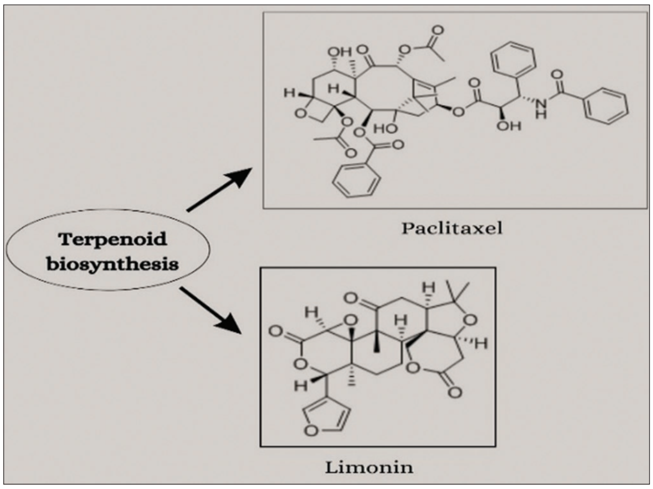

Fig. 10: Production of paclitaxel and limonin through terpenoid biosynthesis pathways

Xiamycins, with antibacterial and antiviral properties, are synthesized by endophytic *Streptomyces* species. They are derived from polyketide pathways, and endophytes offer a sustainable method for their production. Piericidine A and lobophorin A produced from *Streptomyces* species obtained from *Maesa japonica* with antimicrobial and cytotoxic properties [80] are shown in Fig. 11.

Alkaloid biosynthesis

Endophytic fungi of the *Claviceps* genus create ergot alkaloids in their grass host plants. These alkaloids, including ergotamine, play a role in herbivores and pathogen defense [81].

Camptothecin (CPT), a potent anticancer compound, was initially extracted from *Camptotheca acuminata*. Subsequently, endophytic fungi and bacteria, such as *Fusarium solani* and *Aspergillus* species obtained from *Cinnamomum camphora* plants have been identified as alternative, sustainable sources of CPT, reducing dependence on plant sources, such as *C. acuminata* and *Nothapodytes nimmoniana* [82]. These microbes produce similar secondary metabolites, likely due to

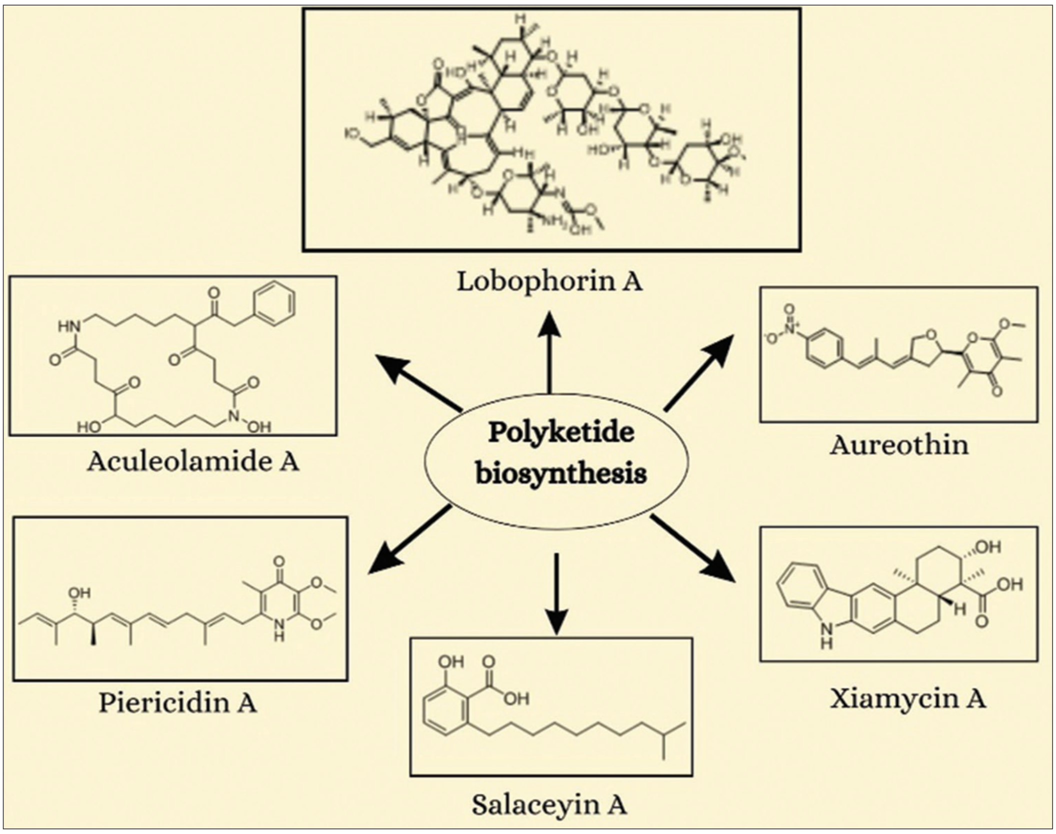

Fig. 11: Production of aculeolamides, salaceyins, aureothin, xiamycins, piericidine A and lobophorin A through polyketide biosynthesis pathways

shared biosynthetic pathways with their host plants. Present research focuses on improving fermentation methods and increasing yields to enhance the production of CPT-derived drugs, such as topotecan and irinotecan, used in cancer therapies [83].

Chaetominine, a bioactive alkaloid obtained from the endophytic fungus *Chaetomium globosum,* extracted from the stem of *Imperata cylindrical,* is characterized by its indole-diketopiperazine structure and significant anticancer and antibacterial effects [84].

Chaetoglobusin U is known for its potent biological effects, such as antifungal, antibacterial, and antitumor activities. Structurally, it features a macrocyclic lactam fused to a perhydroisoindolone core, a feature shared by many cytochalasans [85].

Vincristine, an anticancer alkaloid traditionally extracted from *Catharanthus roseus*, may also be produced by endophytes, such as *Fusarium oxysporum*. These endophytes interact symbiotically with the plant, mimicking or enhancing its metabolic pathways to synthesize vincristine or related compounds are shown in Fig. 12 [86]. Endophytic production offers a sustainable alternative to plant extraction despite lower yields. Research focuses on optimizing fermentation and genetic manipulation to improve scalability. This approach holds promise for sustainable pharmaceutical applications [87].

Phenylpropanoid biosynthesis

Endophytic bacteria from the *Burkholderia* genus may cause host plants to produce phenylpropanoid substances, such as lignin pre-cursors and flavonoids. These substances help plants defend themselves and control their development [88].

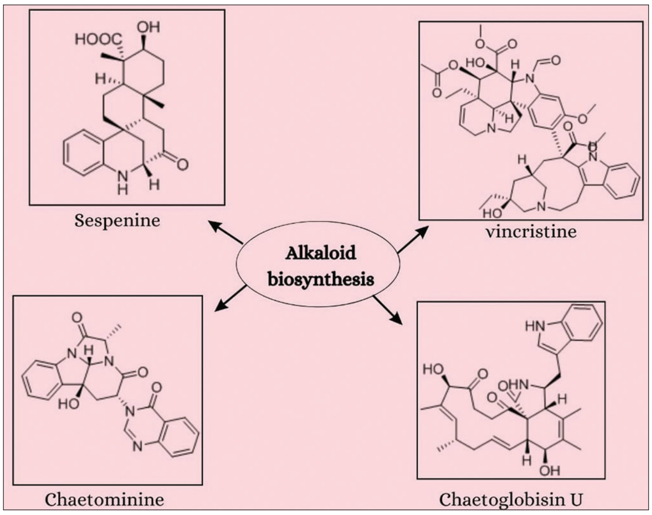

Fig. 12: Production of sespenine, vincristine, chaetominine, and chaetoglobusin U through alkaloid biosynthesis pathways

Traditional *Podophyllum* plants produce podophyllotoxin, a potent anticancer lignan Fig. 13; however, endophytic fungi and bacteria can synthesize it through analogous metabolic pathways. In the phenylpropanoid pathway, phenylalanine ammonia-lyase (PAL) catalyses the conversion of phenylalanine into cinnamic acid, which is then further metabolised to produce compounds like coniferyl alcohol. Coniferyl alcohol undergoes oxidation by peroxidases and laccases to produce pinoresinol, which then converts into secoisolariciresinol, matairesinol, and podophyllotoxin. Symbiotic interactions with plant hosts may enable endophytic fungi, such as *Aspergillus*, *Fusarium*, and *Penicillium*, to mimic these plant processes and get enzymes for podophyllotoxin synthesis [89].

Flavonoid biosynthesis

Endophytic bacteria from *Pseudomonas* species have been demonstrated to increase flavonoid production in *Arabidopsis*. These flavonoids contribute to plant signaling and pathogen defense [90]. Chrysin structure is shown in Fig. 14, a natural flavonoid in plants and endophytic fungi, and presents valuable medicinal and biotechnological potential. Endophytic fungi synthesize chrysin through flavonoid biosynthesis, contributing to its antioxidant, anti-inflammatory, and anticancer properties. Producing chrysin through endophytes offers a sustainable alternative to traditional plant extraction [91]. Furthermore, researchers isolated two kinds of fungus *Aspergillus fumigatus* and *Trichoderma turrialbense* from *Moringa oleifera,* which were responsible in flavonoid biosynthesis [92]. As it is known flavonoids have many activities and effects, especially antioxidant and antibacterial activity [93,94].

Indole alkaloids biosynthesis

Endophytic fungi of the *Aspergillus* species produce indole alkaloids in host plants, including penicillin. These alkaloids have antibacterial characteristics and aid in the fight against infections [89].

Stilbenoid biosynthesis

In grapevine plants, endophytic fungi from the genus *Botryosphaeria* create stilbenoids, such as resveratrol. These chemicals have antioxidant capabilities and aid the plant's defense against infections and environmental stressors [95]. Endophytes play a pivotal role in driving the synthesis of secondary metabolites in host plants through various biochemical pathways. These microorganisms not only enhance the chemical diversity within plants but also significantly contribute to plant defense mechanisms, adaptability to environmental stresses, and interactions with other organisms in their ecosystem.

Biosynthesis of non-ribosomal peptides in endophytic microorganisms

Non-ribosomal peptide synthesis (NRPS) is an enzyme-driven process that produces peptides without ribosomes. These peptides often have essential biological functions, such as antimicrobial, antifungal, and anticancer activities. The modular nature of NRPS allows the incorporation of both standard and non-standard amino acids [96]. Lydiamycins A, JBIR-39, and huoshanmycin are shown in Fig. 15. Endophytic fungi produce antimicrobial peptides. Munumbicins are

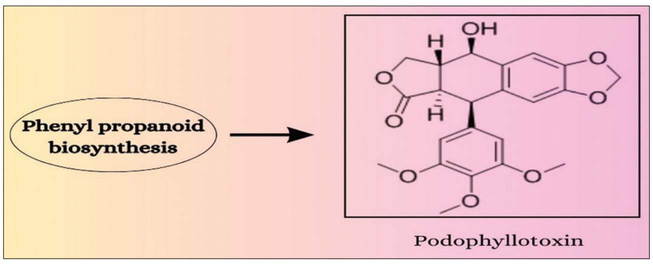

Fig. 13: Production of podophyllotoxin through phenyl propanoid biosynthesis pathways

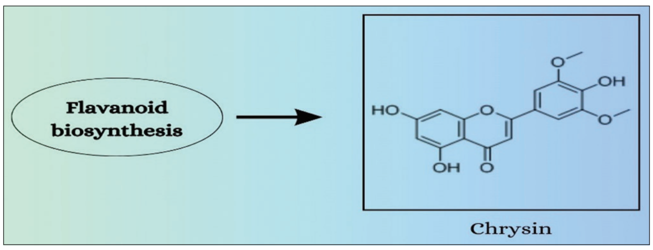

Fig. 14: Production of chrysin through phenyl flavonoid biosynthesis pathways

broad-spectrum antibiotics produced by endophytic *Streptomyces* species [97]. Fusaricidines are cyclic lipopeptides with antibacterial and antifungal properties produced by endophytes, such as *Paenibacillus* species [98].

The following Figs. 16 and 17 depict diverse bioactive compounds produced by endophytes.

SUSTAINABLE PRODUCTION OF PLANT-DERIVED ANTICANCER COMPOUNDS USING ENDOPHYTES

Natural products and other herbal industries suffer from a supply problem

Bioactive secondary metabolites are often obtained in very small quantities (e.g., Vincristine), forcing the industry to collect large quantities of biomass to meet global demand. This method is not sustainable, and hence alternate sources for the natural products, such as synthesis, tissue culture, and endophyte microbes are studied.

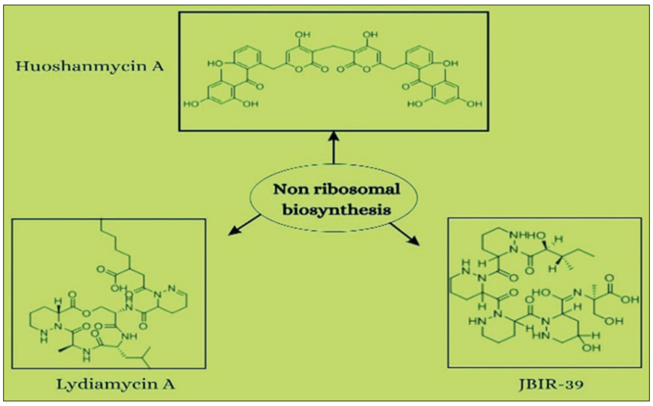

Fig. 15: Production of lydiamycins A, huoshanmycin, and JBIR-39 through non-ribosomal peptide biosynthesis pathways

Endophytic microbes have the following advantages.

- Sustainability: Extracting paclitaxel from yew trees requires harvesting the bark, which often results in the destruction of the tree. Endophytes, by contrast, can be grown in controlled environments, providing an ongoing, renewable source without harming ecosystems.
- Higher efficiency: The yield of paclitaxel from yew bark is extremely low, making it inefficient for large-scale production. Endophytes can produce paclitaxel more efficiently, often leading to higher yields in shorter times under optimized conditions.
- Cost-effective production: Cultivating endophytes in laboratories reduces the need for extensive land use and resources, making it a more economical approach. In addition, the process of growing endophytes and extracting paclitaxel can be scaled up more easily than plant-based methods.
- Environmental impact: Using endophytes reduces the environmental burden associated with deforestation and chemical processes needed to extract paclitaxel from plant materials. This makes it a greener alternative for large-scale drug production.
- Biotechnological improvements: Endophytes can be genetically modified or cultured under optimized conditions to enhance paclitaxel production, providing flexibility and adaptability for future advancements in drug manufacturing [77].

Some of the endophytes as drug sources are studied and briefly discussed in the paragraphs. Tables 1 and 2 highlight the secondary metabolites produced by endophytic bacteria and fungi and details regarding their associated host plants and biological activity.

PACLITAXEL

Paclitaxel, a highly functionalized diterpene, was first isolated from the Pacific yew tree (*T. brevifolia*) in 1971 [138]. It gained significant attention for its potent anti-cancer properties, particularly in treating ovarian, breast, and lung cancers. The mode of action of paclitaxel is unique, as it stabilizes microtubules and prevents their depolymerization during cell division, leading to apoptosis in cancer cells [139]. However, the natural extraction of paclitaxel from yew trees

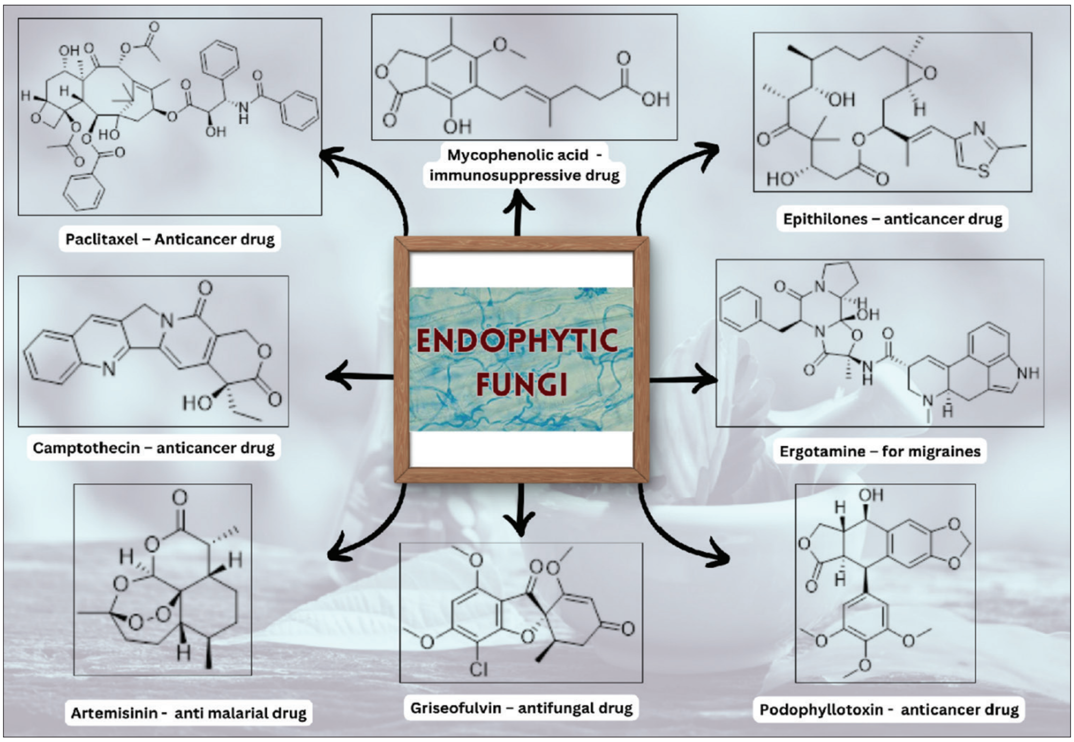

Fig. 16: The endophytic fungus produces compounds with unique structures

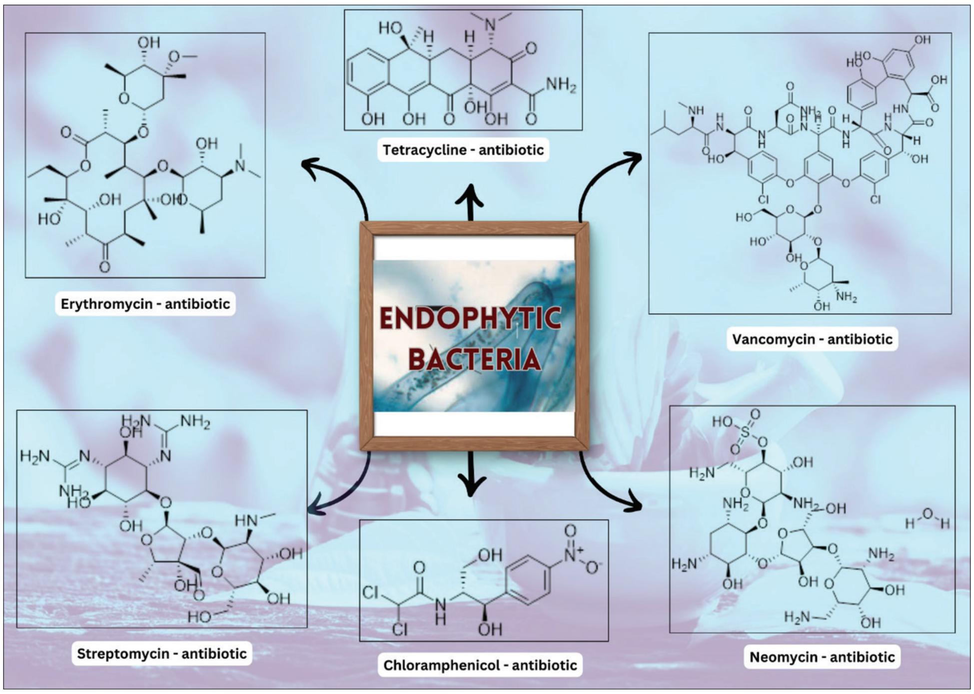

Fig. 17: The endophytic bacteria produce compounds with unique structures

Table 1: The secondary metabolites produced by endophytic fungi are listed in the table

S. No.	Secondary metabolite	Endophytic fungi	Host plant	Biological activity	References
1.	Camptothecin	*Entrophosporain frequent*	*Nothapodytes foetida*	Antitumor	[99]
2.	Camptothecin	*Fusarium solani*	*Camptotheca acuminate*	Anticancer	[100]
3.	Camptothecin	*Fusarium solani*	*Apodytes dimidiate*	Anticancer	[101]
4.	Camptothecin	*TrichodermaatrovirideLY357*	*Camptotheca acuminate*	Anticancer	[102]
5.	Camptothecin	*Nodulisiporium* spp.	*Nethapodytes fortida*	Anticancer	[103]
6.	ChaetoglobosinU	*Chaetomiumglobosum IFB-E019*	*Imperata cylindrical*	Cytotoxic	[85]
7.	ChaetoglobosinX	*C.globosum L18*	*Curcuma wenyujin*	Cytotoxic	[104]
8.	Chaetominine	*Chaetomiumsp IFB-E015*	*Adenophora axilliflora*	Anticancer	[105]
9.	Chrysin	*Alternaria Alternata KT380662*	*Passiflora incarnataL*	Anticancer, Hepatoprotective	[91]
10.	Taxol (Paclitaxel)	*Aspergillus fumigatus TDX105*	*Taxobium distichum*	Anticancer	[105]
11.	Taxol (Paclitaxel)	*Alternaria tenuissima*	*Taxsodiu marhuma*	Anticancer	[106]
12.	Taxol (Paclitaxel)	*Alternaria* spp.	*Ginkgo biloba*	Antitumor	[107]
13.	Taxol (Paclitaxel)	*Bartalinia robillardoides Tassi*	*Aeglumarmeloscorrea ex Roxb*	Anti-cancer	[108]
14.	Taxol (Paclitaxel)	*Cladosporium cladosporio*	*Taxus media*	Antitumor	[109]
15.	Taxol (Paclitaxel)	*Fusarium lateritium*	*Taxusbaccata*	Antitumor	[110]
16.	Taxol (Paclitaxel)	*Pestalotiopsis guepinii*	*Wollemia nobilis*	Antitumor	[110]
17.	Taxol (Paclitaxel)	*Pestalotiopsis microspore*	*Taxus wallichiana*	Anticancer	[111]
18	Taxol (Paclitaxel)	*Pestalotiopsis microspore*	*Taxodium distichum*	Antitumor	[109]
19.	Taxol (Paclitaxel)	*Pestalotiopsis pauciseta*	*Cardiospermum helicacabum*	Antitumor	[112]
20.	Taxol (Paclitaxel)	*Phyllosticta citricarpa*	*Citrus medica*	Antitumor	[112]
21.	Taxol (Paclitaxel)	*Tubercularia* spp.	*Taxus mairei*	Anticancer	[113]
22.	Taxol (Paclitaxel)	*Fusarium oxysporum*	*Rhizophora annamalayana*	Anticancer	[114]
23.	Taxol (Paclitaxel)	*Fusarium redolens*	*Taxus baccata*	Anticancer	[114]
24.	Taxol (Paclitaxel)	*P. terminaliae*	*Terminalia arjuna*	Anticancer	[105]
25.	Taxol (Paclitaxel)	*Taxomyces andreanae*	*Taxus brevifolia*	Anticancer	[110]
26.	Taxol (Paclitaxel)	*Phomopsis longicolla*	*Mesua ferrea*	Anticancer	[115]
27.	Torreyanic acid	*Pestalotiopsis microspore*	*Torreya taxifolia*	Anticancer	[116]
28.	Phenylpropanoids	*Penicillium brasilianum*	*Meliaaze darach*	Anticancer	[117]
29.	Podophyllotoxin	*Alternaria* spp.	*Sabina vulgaris*	Anticancer	[118]
30.	Podophyllotoxin	*Alternaria nee sex*	*Sinopodophyllum Hexandrum*	Antitumor	[119]
31.	Podophyllotoxin	*Aspergillus fumigatus*	*Juniperus communis*	Antitumor	[100]
32.	Podophyllotoxin	*Fusarium oxysporum*	*Juniperus recurve*	Antitumor	[114]
33.	Podophyllotoxin	*Mucorfragilis (TW5)*	*Sinopodophyllum hexandrum*	Anticancer	[120]
34.	Podophyllotoxin	*Phialocephala fortinii*	*Sinopodophyllum hexandrum*	Anticancer	[121]
35.	Podophyllotoxin	*Penicillium implicatum*	*Diphylleiasinensis*	Anticancer	[122]
36.	Podophyllotoxin	*Penicillium implication*	*Dysosma veitchii*	Antitumor	[123]
37.	Podophyllotoxin	*Phialocephala fortinii*	*Podophyllum peltatum*	Antitumor	[121]
38.	Podophyllotoxin	*Trametes hirsute*	*Podophyllum hexandrum*	Antitumor	[124]
39.	Vincristine	*Fusarium oxysporum*	*Catharanthus roseus*	Antitumor	[125]

Table 2: The secondary metabolites produced by endophytic bacteria

S. No.	Secondary metabolite	Endophytic bacteria	Host plant	Biological activity	References
1.	Aculeolamides	*Streptomyces aculeolatus MS1-6*	*Musa sapientum L.*	Anti-inflammatory and antioxidant	[126]
2.	Aureothin	*Streptomyces* spp. *AE170020*	*Pinus densiflora*	Nematicidal	[78]
3.	Coronamycin	*Streptomyces* spp. *MSU-2110*	*Monstera sp*	Anti-fungal, anti-malarial.	[127]
4.	Fusaricidins	*Paenibacillus polymyxa*	*Dendrobium nobile*	Anti-fungal	[128,129]
5.	Huoshanmycins	*Streptomyces* spp. *HS-3-L-1*	*Dendrobium huoshanense*	Cytotoxic	[130]
6.	JBIR-39	*Streptomyces* spp. *AB100*	*Atropa belladonna L.*	Anti-bacterial	[131]
7.	Limonin	*Bacillus* spp. *P*	*Citrus maxima (Burm.)*	Neuroprotective	[75,132]
8.	Lobophorins	*Streptomyces olivaceus JB1*	*Maesa japonica (Thunb.)*	Anti-inflammatory, cytotoxic	[80]
9.	Lydiamycins A, E -H, Cyclodepsipeptides	*Streptomyces* spp. *HBQ95*	*Cinnamomum cassia Presl*	Anti-mycobacterial, antimetastatic	[133]
10	Munumbicins	*Streptomyces* spp. *30562*	*Kennedia nigriscans*	Anti-bacterial	[97]
11.	Piericidins	*Streptomyces* spp. *KIB-H1083*	*Diphasiastrum veitchii*	Anti-bacterial, cytotoxic	[134]
12.	Salaceyins	*Streptomyces Laceyi*	*Ricinus communis L.*	Anti-fungal, cytotoxic	[135]
13.	Sespenins	*Streptomyces* spp. *HKI0595*	*Kandelia candel*	Anti-bacterial, cytotoxic	[136]
14.	Xiamycins	*Streptomyces* spp. *GT2002/1503*	*Bruguiera gymnorrhiza*	Anti-HIV activity	[137]

is unsustainable, requiring the destruction of large numbers of slow-growing trees to meet global demand [140].

As an alternative, researchers have turned to endophytic fungi as a potential source of paclitaxel. These fungi live symbiotically within plants and have demonstrated the ability to produce secondary metabolites, including paclitaxel. The discovery of *Pestalotiopsis microspora*, an endophytic fungus isolated from the inner bark of the Himalayan yew (*Taxus wallichiana*), marked a breakthrough in paclitaxel production. This fungus was shown to produce paclitaxel in culture, offering a sustainable method for large-scale drug production without relying on tree harvesting [141].

CPT

CPT is a monoterpene indole alkaloid recognized for its potent anticancer properties, discovered in 1966 [142]. It inhibits the enzyme DNA topoisomerase I, which plays a crucial role in DNA replication and repair, making it effective against several cancers, such as lung, ovarian, and colorectal cancers [143]. Initially sourced from *C. acuminata* (Chinese tree), CPT has been found in other plant species and endophytes. However, overharvesting of these plants has led to their depletion, sparking interest in biotechnological methods for sustainable production [82].

CPT is produced primarily by plants, but it can also be synthesized by endophytes, such as *F. solani*, *Neurospora crassa*, and *Aspergillus* species. The alkaloid is notably found in *C. acuminata* and *N. nimmoniana*. However, the content of CPT in these plants is low, and harvesting large quantities of plant material is required to meet market demands [142].

The global demand for CPT and its derivatives has surged, but natural sources have become unsustainable due to slow plant growth rates and overharvesting. This challenge has prompted extensive research into alternative production methods, including plant tissue cultures, endophyte cultivation, and metabolic engineering [99].

Producing 1 ton of CPT requires roughly 1,000 to 1,500 tons of plant material, making it highly resource-intensive. This unsustainable practice has led to a significant decline in natural populations of *C. acuminata* and *N. nimmoniana.* This has led researchers to explore biotechnological methods, such as cell suspension cultures, callus cultures, and organ cultures to increase yields without depleting natural plant populations [143].

PODOPHYLLOTOXIN

Historical use and traditions recognition: *Podophyllum* species were utilized by Native Americans for their antimicrobial and anthelmintic properties [144]. In the 19th century, it became part of Western medicine as a purgative but was eventually restricted due to toxicity risks [145]. Modern science rediscovered its value in cancer therapy, particularly for topical treatments, bringing it back into pharmaceutical use in the mid-20th century with controlled applications [146].

Podophyllotoxin, a plant-based lignan, holds significant medical value, especially for its anticancer effects. Originally sourced from the *Podophyllum* genus and related plants, such as *Juniperus* and *Linum*, it has been a focus of drug development [122]. Due to the ecological impact of harvesting these plants and challenges in consistent cultivation, scientists are exploring alternative ways to produce podophyllotoxin. One promising avenue is using endophytic fungi, which reside within plant tissues and have shown potential to synthesize the compound independently [147].

Limitations in natural sourcing: The demand for podophyllotoxin has led to concerns over the sustainability of *Podophyllum* plant populations. Harvesting is costly and unsustainable at large scales. This has led researchers to investigate endophytic fungi as alternative producers of podophyllotoxin, with several strains identified that produce the compound *in vitro*. Fungi from plants, such as *Dysosma versipellis* and *Juniperus communis* have been successfully cultured to yield podophyllotoxin under laboratory conditions [148].

Advances in endophytic production research are underway to optimize podophyllotoxin production through endophytic fungi by adjusting growth conditions and adding elicitors that increase yield. For example, certain treatments applied to fungi from *S. emodi* plants have significantly enhanced podophyllotoxin synthesis. These findings point to a promising direction for sustainable, large-scale production [14].

Future Directions For podophyllotoxin to be produced at a commercial scale through endophytes, further developments in fermentation and bioengineering techniques are needed. A successful transition to these methods would not only ensure a stable supply for anticancer drug production but also relieve pressure on natural plant populations, promoting conservation [14].

VINCRISTINE

The production of vincristine, an essential chemotherapy medication extracted from *C. roseus*, is hindered by several factors, including limited natural availability, ecological issues, and expensive plant extraction methods. To overcome these obstacles, scientists are investigating biotechnological solutions focusing on utilizing endophytic fungi. Research has demonstrated that certain endophytic fungi, such as

F. oxysporum and *Alternaria* species, isolated from *C. roseus* have exhibited the capability to synthesize vincristine or related alkaloids under controlled laboratory settings [149].

CONCLUSION

Endophytes are being explored for their potential to produce bioactive compounds, which could have applications in agriculture, medicine, and industry. These compounds exhibit potent biological activities and can be used as alternatives to conventional pesticides, pharmaceuticals, and industrial chemicals. The unique microenvironment within plant tissues offers a rich source of novel metabolites, that researchers can harness to create sustainable solutions. The study of endophytes also highlights the importance of biodiversity conservation, as many endophytic species remain unexplored. Valuable resources can be discovered for future biotechnological innovations by preserving natural habitats and studying microbial communities. The study of endophytes for bioactive compound production is a dynamic field with significant implications for agriculture, medicine, and biotechnology. It can potentially revolutionize industries while promoting environmental sustainability and biodiversity conservation.

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AUTHOR CONTRIBUTIONS

Shobha Singarapalle: Conceptualized the study and drafted the manuscript. M. Abdullah Harh: provided expertise in pharmacognosy and contributed to manuscript review. Cheepuri Gowtham Phanindra: Reviewed the manuscript to ensure scientific accuracy. D. Jagadeeswara Reddy: Reviewed the article, focusing on biotechnological aspects. Patrick Francis Kimariyo: Assisted in reviewing and refining the manuscript. Murali Krishna Kumar Muthyala: Supervised the study, contributed to the review process, and provided final approval of the manuscript.

DECLARATION OF INTEREST

The authors declare no conflicts of interest. They take full responsibility for the accuracy and integrity of the content presented in this manuscript.

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