



AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: <http://www.ajptr.com/>

Endophytes: A Future Prospective to Drug Development

Pranita Sunar*

Assistant Professor, Department of Pharmacognosy, Mata Gujri College of Pharmacy, Mata Gujri University, Kishanganj, Bihar, India, 855107.

ABSTRACT

Endophytes are microscopic creatures that live as parasites in living plant body without affecting their host plant. These organisms may be fungi, bacteria or any other microbes that lives in various parts of the host plants such as the stems, roots, or leaves and other sections. Endophytes coexist in symbiotic relationships with their host plants, frequently offering advantages including improved growth, tolerance to environmental stresses and better resistance to disease. They are the kind of microorganism which has the potential to biosynthesise medicinally active substances called secondary metabolites. The discovery of secondary metabolites in diverse sources resulted in the development of medications intended to cure illnesses in humans. Novel secondary metabolic products with significant pharmacological value will be introduced by routine screening of natural resources. Many important bioactive compounds have been effectively discovered from endophytic fungi having cytotoxic, antimicrobial, insecticidal, anticancer and antioxidant activities. In this review, we attempt to summarize the endophytes-host relationship and the mechanism by which they are capable to produce secondary metabolites as their host plant and their utilization in development of new drugs.

Keywords: -Endophytes, bioactive, secondary metabolites, biosynthesis, drug development.

*Corresponding Author Email: pranita.mgcop@gmail.com

Received 22 July 2025, Accepted 19 August 2025

Please cite this article as: Sunar P., Endophytes: A Future Prospective to Drug Development. American Journal of PharmTech Research 2025.

INTRODUCTION

Secondary metabolites are organic compound produced mainly by plants for their protection against various environmental stresses and predators. The goodness of secondary metabolites has been exclusively harvested by man kind to boost their health, to expand the base of the nutritional pyramid for a healthy diet and also to increase the agricultural productivity enhancing the economics of our society in a certain positive way [1]. In recent studies, researchers have found that the secondary metabolites are also produced by the symbiotic microorganisms called endophytes. Endophytes are microscopic organisms that parasitize living plants and exist there without harming their host plant. These microorganisms could be bacteria, fungi, or any other type of microbe that inhabits different portions of the host plant, like the stems, roots, leaves, or other regions. They live in symbiotic relationships with their host plants, often providing benefits including enhanced growth, increased resilience to environmental stressors, and enhanced resistance to disease.

The isolation of secondary metabolites from endophytes represents a burgeoning area of research with profound implications for drug discovery, agriculture, and biotechnology. The ability of endophytes to biosynthesize a wide variety of secondary metabolites with distinct chemical structures and biological functions has drawn attention in today's research area clarifying these compound's biosynthesis processes and pharmacological characteristics is of great interest because of their enormous potential as sources of innovative medicines, biocontrol agents, and crop enhancers [2].

The metabolic capacities of endophytic communities are further shaped by the co-evolutionary processes between endophytes and their host plants, which provide a huge pool of unexplored natural products that are still awaiting identification and characterization. To fully use endophyte derived chemicals, it is imperative to comprehend the mechanisms underpinning endophyte-plant interactions and the ecological conditions regulating the generation of secondary metabolites. The isolation of secondary metabolites from endophytes typically involves a series of steps, starting with the selection and cultivation of endophytic strains from plant tissues [3].

History

German botanist Johann Heinrich Friedrich Link initially described endophytes in 1809. There is a great diversity among endophytic organisms; very few endophytes have been thoroughly studied. The isolation of secondary metabolites from endophytes has been a significant area of research in the field of natural products chemistry. Endophytes are microorganisms that live within plant tissues without causing harm to the host plant. They have been found to produce a wide variety of

bioactive compounds with potential pharmaceutical, agricultural, and industrial applications [4]. It was traditionally believed that endophytic fungi could only create secondary metabolites that were produced by their plant hosts. However, studies have demonstrated otherwise. These metabolites may only be produced by endophytes, or they may be produced by both endophytes and plants after the necessary genes are transferred from endophyte to plant or vice versa [5]. One of the earliest documented instances of isolating secondary metabolites from endophytes dates back to the 1990s. When scientists started looking into the microbial biodiversity of plants, they found that endophytes could produce both distinct chemicals that were not present in the host plant and compounds that were comparable to those found in the host plant [6]. One of the most well-known instances of endophytic fungal-derived compounds being discovered is *Taxomyces andreanae*, a fungus that was isolated from *Taxus brevifolia*. Taxol or paclitaxel (a potent anticancer medication) is the product of *T. andreanae* productions [5] Many studies conducted over the years have concentrated on separating and describing secondary metabolites from endophytes derived from different plant species. Alkaloids, terpenoids, phenolics, and peptides are a few examples of these metabolites. Similarly, the alkaloid camptothecin, used in cancer treatment, was first discovered in the endophytic fungus *Fusarium solani* from the Chinese Happy Tree (*Camptotheca acuminata*) [7].

Table 1 shows the various endophytes, their respective host plants and secondary metabolites produced by them [8-16].

Table 1. Examples of Plant Secondary Metabolites produced by endophytes and their host plants.

Serial No.	Endophytic species	Host Plant	Secondary metabolite
1.	<i>Alternaria Sp.</i>	<i>Taxus cuspidata</i> <i>Taxus chinensis</i> <i>Ginkgo biloba</i> <i>Xylariapsidii</i>	Taxol Resveratrol
2.	<i>Aspergillus fumigatus</i>	<i>Juniperus communis</i>	Podophyllotoxin
3.	<i>Fusarium oxysporum</i>	<i>Juniperus recurve</i> <i>Catharanthus roseus</i>	Podophyllotoxin Vincristine
4.	<i>Taxomyces andreanae</i>	<i>Taxus brevifolia</i>	TaxolPI
5.	<i>Fusarium proliferatum</i>	<i>Macleaya cordata</i>	Rohitukine
6.	<i>Entrophosporainfrequens</i>	<i>Nothapodytes foetida</i>	Camptothecin
7.	<i>Penicillium oxalicum</i>	<i>Gymnemasylvestre</i>	Gymnemagenin
8.	<i>Eupenicillium parvum</i>	<i>Azadirachta indica</i>	Azadirachtin A & B
9.	<i>Alternaria sp.</i>	<i>Capsicum annum</i>	Capsaicin
10.	<i>Pestalotiopsis microspora</i>	<i>Taxus cuspidata</i> <i>Taxus wallichiana</i>	Taxol

Mechanism of Production of Secondary Metabolites by Endophytic Organism

In this article, we examine whether the proximate mechanistic foundation for endophytes' production of plant secondary metabolites is sufficiently understood. According to earlier research, the endophyte's ability to manufacture the host's secondary metabolite may be due to horizontal gene transfer between the host and the organism [17]. Nevertheless, there isn't any solid data to back up this theory as of yet [18]. Here, we provide an overview of our understanding of how endophytes produce plant secondary metabolites by taking some medicinally important bioactive compounds as example.

1. Taxol

Taxol, often known as paclitaxel, the highly oxygenated diterpenoid natural product, was initially extracted from the Pacific Yew Tree (*Taxus brevifolia*). It is among the most frequently used anticancer medications. Soon after its distinct method of action was discovered and its great demand arose, a thorough quest was launched to find substitutes for the slow-growing and limited Pacific yew. Taxol is biosynthesized by various plant species as shown in Table 1.

Taxol is produced in plants via the plastidial methylerythritol phosphate route [19], which entails cyclization of geranyl-geranyl pyrophosphate to generate taxa-4(5),11(2)-diene. The production of taxol in plants occurs in multiple cellular compartments, including the plastids, endoplasmic reticulum, and cytoplasm [20]. There have been numerous attempts to decipher the biosynthesis route of taxol in endophytes. Some researchers have found that the gene 10deacetylbaaccatin-III-10-O-acetyl transferase (DBAT) was amplified by PCR from the taxol producing endophyte *Cladosporium cladosporioides*. Baaccatin III is produced by the DBAT, which also catalyzes the last diterpene step in the taxol biosynthesis pathway. [21-22]. Taxadiene synthase, a gene was found to be present on another taxol producing fungal endophytes called *Pestalotiopsis species* isolated from *Taxus cuspidata*. The recent study reveals paclitaxel biosynthetic gene in *Penicillium aurantiogriseum* suggesting independent evolution and unlikely horizontal gene transfer between the endophytic fungus and its host plant. Some researchers suggested that taxol obtained from endophytes may be a carryover from the host tissue from where they were separated. Endophytic fungi create plant secondary metabolites in culture media for numerous generations and do not transfer detectable amounts between cultures [23].

2. Camptothecin

Camptothecin is a well-known monoterpene indole alkaloid with broad-spectrum anti-cancer action. Owing to the fact that plants are not as productive or efficient as other sources of camptothecin, endophytes have the ability to meet the enormous market demand of the

pharmaceutical industry due to their rapid growth, high cost- effectiveness, good reproducibility [24].

Camptothecin is a quinoline alkaloid obtained from different plant sources such as *Nothapodytes nimmoniana*, *Ophirohiza mungos*, *Eravatamia heyneana* and *Mostueabrunon* are camptothecin compound first isolated from *Camptotheca acuminata* by Wall and Wani in 1960[25]. Due to its distinct method of action, which involves selectively inhibiting DNA topoisomerase I, camptothecin demonstrated strong anticancer efficacy and generated a great deal of interest globally. As of now, camptothecin is the most well-known candidate for the creation of novel anticancer medications.[26]

3.Podophyllotoxin

Podophyllotoxin is a natural product derived from plant extracts, is currently a pharmaceutical in high demand for anticancer drug therapies. Podophyllotoxin is often used in medicine, particularly in the treatment of genital warts caused by the human papillomavirus. It's derived from certain plant species such as *podophyllum* [26]. Numerous well-known antitumor medicines, including teniposide, etoposide, and *etopophos*, are synthesized using it as a precursor [27]. Podophyllotoxin's ability to alter the cellular cytoskeleton and inhibit reverse transcriptase allows it to treat viral infections like condyloma acuminatum. [28].

Podophyllotoxin is an aryltetralin-type lignan isolated from various *Podophyllum* species. The two most prevalent sources are the rhizomes of *Podophyllum peltatum* and *Sinopodophyllum hexandrum* Royle. These perennial herbs are abundantly found throughout the Himalayan area and Western China. Plants with high podophyllotoxin or podophyllotoxin-analogue content have been widely employed in traditional medicine for a long time in various cultures.[29] Its compound show the anti-inflammatory, anti-fertility, Anti-implantation, anti-cancer and immunomodulatory properties.

Juniperus communis (common juniper) hosts *Aspergillus fumigatus* as an endophyte, the production of podophyllotoxin by the fungus within the plant occurs through a fascinating symbiotic relationship. Podophyllotoxin is synthesized by the fungus using a type II polyketide synthase (PKS) mechanism. Type II PKS enzymes typically assemble aromatic polyketides through iterative cycles of decarboxylative condensation of malonyl-CoA extender units with a starter molecule. In the case of podophyllotoxin, the process involves specific enzymes within the fungus that catalyses these reactions to produce the final compound. The symbiotic relationship between *Aspergillus fumigatus* and podophyllotoxin production holds promise for biotechnological

applications, including the potential development of novel pharmaceuticals or biopesticides derived from natural sources.[30]

4.Rohitukine

The chromone alkaloid rohitukine was first identified as originating from *Amoora rohituka*. Rohitukine has immunomodulatory and anti-inflammatory qualities. It has been investigated to alter the structure of rohitukine in order to increase its anti-implantation activity. It also demonstrates cytotoxic efficacy against HL-60 promyelocytic leukemia and HCT-116 colon cancer cell lines, as well as attenuating peptic ulcers in rat models. Studying the structure-activity relationship of rohitukine to improve its anticancer efficacy resulted in the creation of flavopiridol. Strong cytotoxic action against a variety of cancer cell lines is exhibited by flavonopril. The European Medicines Agency recently approved it to treat chronic lymphocytic.[31]

Rohitukine is a natural product with promising anticancer properties, originally isolated from the Indian medicinal plant *Dysoxylum binectariferum*. Endophytes are microorganisms that live within plant tissues without causing harm. Researchers have explored the potential of endophytes to produce bioactive compounds similar to those found in their host plants, including Rohitukine.[32] It is known that endophytic fungi found in *Macleaya cordata* are capable of producing rohitukine, a naturally occurring alkaloid with promising therapeutic applications. The anti-cancer effects of rohitukine have been investigated; in particular, its capacity to block specific enzymes involved in cell division has been noted. Because of this, pharmacological research on *Macleaya cordata* and its endophytes is interesting for possible medicinal uses. [33]

Macleaya cordata hosts *Fusarium proliferatum* as endophytes the production of rohitukine in the mechanism of genetic and epigenetic regulation. *Uranium entophytes* can alter gene expression patterns in the host plant. This may involve direct regulation of genes encoding enzymes involved in rohitukine biosynthesis, as well as epigenetic modifications that affect chromatin structure and gene accessibility.[34]

5.Resveratrol

Resveratrol is a natural polyphenol from the stilbene family. It consists of two benzene rings connected by an isopropyl moiety and separated by a double bond [35]. Resveratrol was first found in the 1940s from the roots of *Veratrum grandifolium* (White hellebore) and later in the 1960s from *Polygonum cuspidatum*, which was traditionally utilized in Chinese and Japanese medicine [36]. Resveratrol's medical benefits gained attention after it was discovered that despite a high intake of saturated fats in French cuisine, the French population had low rates of coronary heart disease. This finding became known as the "French paradox". Red wine contains resveratrol,

which has been linked to cardioprotective effects [4]. Additionally, it exhibits anti-cancer, anti-inflammatory, anti-diabetic, and anti-aging characteristics [37]. Resveratrol is recognized as a beneficial chemical in agriculture, medicine, food, and cosmetics. Resveratrol has unique antifungal properties against *Botrytis cinerea*, a major fungal disease in grapevines [38]. Since its discovery, resveratrol has been a highly sought-after molecule by researchers due to its exceptional qualities. Resveratrol can be found in a variety of foods, including chocolate, tea, pea-nuts, grapes, and other berry species. Currently, the commercial extraction of resveratrol from *Polygonum cuspidatum* roots is a costly and time-consuming procedure. Also, when the plant is completely destroyed, this can have a detrimental effect on the environment. Many methods have been used to increase the synthesis of secondary metabolites, such as plant cell culture technology, which involves growing cells in bioreactors to generate a secondary metabolite by the use of STS gene transformation, and hairy root culture [39]. On the other hand, this method's major drawback is its genomic instability, which silences a number of other gene clusters [40].

Xylaria psidii hosts *Aspergillus fumigatus* in endophytes to the production of resveratrol in the mechanism of endophytic colonization. *Xylaria psidii* establishes itself as an endophyte by entering and colonizing the internal tissues of host plants. This colonization process involves fungal adaptations that allow it to evade or suppress the plant's immune responses, ensuring survival within plant cells.[41]

6. Capsaicin

Capsaicin is a natural compound found in chili peppers, responsible for their spicy heat. It binds to pain receptors in the mouth and skin, causing a burning sensation. It's often used in food to add heat and flavour, and also has applications in topical creams for pain relief. Capsaicin is primarily obtained from chili peppers, which are the fruits of plants belonging to the genus *Capsicum*. [42] These include various species such as *Capsicum annuum* (bell peppers, chili peppers), *Capsicum frutescens* (tabasco peppers, cayenne peppers), and others. Capsaicin is found in the fruits, particularly in the seeds and the membranes inside the peppers. Endophytes, as microorganisms living within plant tissues, have been explored for their potential to produce various bioactive compounds, including capsaicinoids like capsaicin. Isolating capsaicin from endophytes presents potential advantages such as sustainable sourcing, as well as the possibility of discovering novel derivatives or analogues of capsaicin with varied pharmacological properties. This approach also contributes to understanding the biosynthetic pathways and ecological roles of capsaicin in plants and associated microorganisms [43].

The production of capsaicin in capsicum plants, which takes place in specific cells of the placental tissue, is well understood. But if we were to speculate on a possible process by which endophytes produce capsaicin [44].

Capsicum annum hosts *Alternaria sp* in endophytes for the production of Capsaicin with the mechanism of genetic and epigenetic regulation. *Alternaria* endophytes induce changes in the expression of plant genes related to secondary metabolite biosynthesis. This includes direct regulation of gene transcription and potential epigenetic [45].

7. *Gymnemagenin*

Gymnemagenin, a bioactive compound extracted from the leaves of *Gymnema sylvestre*, has garnered attention for its potential health benefits. *Gymnema sylvestre*, a plant native to India and Africa, has been traditionally used in Ayurvedic medicine for its properties related to blood sugar regulation. Gymnemagenin specifically is believed to contribute to these effects by influencing glucose metabolism and insulin function. As a result, it has been incorporated into dietary supplements aimed at supporting metabolic health and potentially aiding in the management of conditions like diabetes [46].

Penicillium oxalicum is a fungal species known for its ability to produce various secondary metabolites, but specific information on its production of Gymnemagenin is limited in current literature. The triterpenoid saponin known as gymnemagenin is usually extracted from the plant *Gymnema sylvestre*, which is well-known for its therapeutic qualities. If the pathways for expressing the genes required for Gymnemagenin production are present in *Penicillium oxalicum*, then genetic engineering or other biotechnological methods would be required to extract Gymnemagenin from the fungus [47].

Gymnema sylvestre is a plant containing the triterpenoid gymnemagenin, which is used in the pharmaceutical industry as an antidiabetic agent. The objective of this study was to determine whether endophytic fungi, isolated from *G. sylvestre*, produce gymnemagenin. We isolated an endophytic fungal strain from the leaves of *G. sylvestre* which produces gymnemagenin in the medium. The fungus was identified as *Penicillium oxalicum* based on morphological and molecular methods [48].

Gymnema sylvestre hosts *Penicillium oxalicum* in endophytes to the production of gymnemagenin with the mechanism of endophytic relationship. *Penicillium oxalicum* resides within the tissues of *Gymnema sylvestre* as an endophyte. Endophytes often establish symbiotic relationships with their host plants, where they exchange nutrients and chemical signals [49].

8. Vincristine

Vincristine is a potent chemotherapy medication primarily used in the treatment of various cancers, including leukemia, lymphoma, and some solid tumours. It belongs to a class of drugs known as vinca alkaloids, which are derived from the Madagascar periwinkle plant (*Catharanthus roseus*).[50]

It is a plant that is home to hundreds of such endophytic microbes. It is also called Vinca rosea, madagaskar periwinkle, cape periwinkle, old maid, sadabahar, etc. It belongs to the family Apocynaceae, whose members are most commonly used for their medicinal properties. *Catharanthus roseus* is traditionally used to treat diabetes. This plant has anticancer, antidiabetic, anti-alzheimer, and wound-healing properties [3,6]. It is also known to produce a variety of terpenoid indole alkaloids such as vincristine, vinblastine, catharanthine, ajmalicine, vindoline, etc. which are of immense importance in the medical industry [51]

Catharanthus roseus hosts *Fusarium oxysporum* for the production of Vincristine with the mechanism of endophytic relationship. *Fusarium oxysporum* establishes a symbiotic relationship as an endophyte within *Catharanthus roseus*. Endophytes like *Fusarium oxysporum* reside within plant tissues without causing apparent harm and can contribute to the plant's secondary metabolism.[52]

9. Azadirachtin A & B

Azadirachtin A and B are prominent bioactive compounds derived from the seeds of the neem tree (*Azadirachta indica*), a plant native to the Indian subcontinent and widely cultivated in tropical and subtropical regions worldwide. These compounds belong to the chemical class of limonoids, which are characterized by their complex structure and diverse biological activities of insect growth regulation, antifeedant activity, low toxicity to mammals etc [53].

Azadirachta indica is also referred to as neem. It is a member of the Meliaceae family. This plant exhibits a variety of detrimental effects on insects in all of its sections, such as ovipositor deterrent, anti-feedant, and other inhibitory properties. Several hundred compounds have been identified from different sections of the neem tree. And most of the active principles belong to the group of tetranortriterpinoids especially "Azadirachtin" and its Analogues [54].

Azadirachta indica hosts *Eupenicillin parvum* to the production of azadirachtin A&B with the mechanism of Enzymatic. Biosynthesis of azadirachtin A and B involves a series of enzymatic reactions catalysed by specific enzymes produced by *Eupenicillium parvum*. These enzymes include polyketide synthases (PKSs), which are involved in the formation of the polyketide backbone of azadirachtins, as well as other modifying enzymes that introduce structural [55].

Biological Activity of the Endophytic Fungal Secondary Metabolites

Endophytic Fungi are highly skilled in the synthesis of a wide range of pharmacologically significant compounds with great therapeutic potential, such as compounds with antiviral, antifungal, antibacterial, anticancer, and anti-cancer properties. Different EFs have the ability to provide hormones and plant growth factors. It has been shown that a variety of extracellular enzymes, including phosphatase, which changes insoluble phosphates into soluble forms for simpler plant absorption, are released by some endophytes. They boost the immune system of the host, lessening the severity of infections and the harm that pathogenic microbes can inflict [56,]. Plants produce a variety of biomolecules through their biocontrol systems, which protect them from potentially fatal infections and promote their growth [57].

Antibiotics:

The production of antibiotics via metabolic pathways is commonly recognized as a successful approach to safeguarding plants from disease. Many bioactive compounds have the ability to suppress phytopathogens, although few of these have been thoroughly studied [58]. Numerous metabolites were created by endophytes, the majority of which have antimicrobial qualities. Alkaloids, flavonoids, peptides, phenols, polyketides, quinones, steroids, and terpenoids are some of these metabolites [59]. 2, 4-diacetyl phloroglucinol is a phenolic antibiotic with a wide range of action that has demonstrated *Pseudomonas spp.* It supports the biological regulation of plant diseases, especially those that are soil-borne.[60].

Anti-cancer activity:

Cancer is the second leading cause of death globally due to its high incidence rate. Malignant cells kill 15 million people annually, and the number is increasing. Endophytic organisms provide safe, biocompatible, less toxic, and more resistant natural compounds that can treat cancer. Natural chemicals offer cancer treatment alternatives to chemotherapeutic drugs. These natural compounds have anti-cancer properties and can effectively treat many cancers. Their abundance makes them suitable for cancer treatment. Endophytic fungi like *Taxomyces andreanae*, *Seimatoantlerium nepalense*, *Alternaria alternative* have been connected to the synthesis of paclitaxel, an anti-cancer medication [61]. It attaches to tubulin, preventing depolymerization during cell division. Taxol from sick chilli plant fruits demonstrated cytotoxic effect against human cell lines MCF-7, HLK-210, and HL-251. Endophytes *Sinopodophyllum hexandrum* and *Dysos maveitchii* produce podophyllotoxin, which is used to treat leukemia, testicular, prostate, lung, and ovarian cancers[62].

Anti-diabetic activity:

Endophytic fungi may produce anti-diabetic compounds, according to recent studies. *Nigrosporaoryzae*, an endophytic fungus found in *Combretum dolichopetalum* leaves, has been shown to reduce fasting blood sugar in diabetic rats when purified components are administered [63]. Chemicals used include abscisic acid, 70-hydroxy abscisic acid, and 4-deshydroxyl alter-solanol. The endophytic fungus Xylariaceae spp. produces 8-hydroxy-6,7-dimethoxy-3-methyl isocoumarins, which have a high glucosidase inhibitory effect. Oral administration of glucose and alloxan to Wistar albino rats combined with *Salvadoraoleoides* extracts from *Phoma spp.* and *Aspergillus spp.* resulted in anti-diabetic and hypolipidemic effects [64]. Bioprospecting has identified endophytic fungi from medicinal plants, including *Rauwolfia densiflora* and *Leucas ciliata*, as potential diabetic therapies. Compounds produced by *Fusarium spp.* and *Alternaria spp.* Have been shown to have anti-diabetic properties, indicating that these fungal endophytes could provide multifunctional therapeutics [65].

Anti-malarial activity:

New malaria therapy medications are urgently needed due to the fast rise of anti-drug resistant malaria parasites in recent years. Munumbicins E-4 and E-5, produced by endophytic fungi, were found to have twice the anti-malarial activity of chloroquine [58]. *Diaporthemiriciae*, an endophyte, produces the secondary metabolite epoxy cytochalasin H. This chemical effectively suppresses *Plasmodium falciparum*, a malaria strain that is resistant to chloroquine [66]. Endophyte species *Paecilomyces lilcinus* and *Penicillium janthinellum* have been identified as potential sources of novel chemicals with anti-*Plasmodium falciparum* activity for malaria treatment. Endophytic fungus, including *Aspergillus niger*, *Fusarium spp.*, and *Nigrospora spp.*, can produce bioactive chemicals that inhibit *Plasmodium falciparum* [67].

Antiviral action:

Endophytic fungi have been shown to produce effective antiviral medications against several viruses, including HIV [68]. Two new compounds, cytonic acid A and cytonic acid B, that are isolated from *Cytonaema spp.*, have been shown to have antiviral action. The structures of preside isomers were determined by nuclear magnetic resonance and mass spectrometry, which helped identify new inhibitors of the human cytomegalovirus's pro-tease activity. The antiviral compound Hinnuliquinone is produced by fungal endophytes in the phyllo sphere (leaves) of oak trees (*Quercuscoccifera*), and it has been connected to the suppression of HIV-1 protease activity [65]. *Thetenuissima alternaria* an endophytic fungus produces altertoxins, which have strong anti-HIV-1 properties. Numerous additional compounds isolated from *Emericella spp.* (HKZJ) have been discovered to have antiviral activity against the influenza A virus (H1N1), in addition to

emerimidines (A, B), dehydroaustin, austinol, aspernidine (A, B), austin, emeriphenolicins (A, D), and acetoxydehydroaustin [69]. Even in their most basic forms, the majority of therapeutic plant mixes have a comparatively significant antiviral activity. It has been shown that some actinomycetes have antiviral action. 2-(furan-2-yl)-6-(2S, 3S, 4-trihydroxybutyl) pyrazine is an antiviral compound that was first isolated from the plant species *Jishengella endophytica*. This substance is sufficient to stop the influenza A (H1N1) virus from spreading [58].

CONCLUSION

Endophytes are a type of microbial resource that is widespread and has a large species diversity. According to recent research, endophytes that stimulate the synthesis of secondary metabolites in their hosts not only cause their hosts to produce more substances, but also set off a sequence of physiological reactions that control stress tolerance and host growth. Endophytes serve as both natural medication replacements and seed banks for novel active metabolites, supporting host growth and development. Nonetheless, there are still a lot of unanswered questions regarding the lives and mechanisms of endophytes in research because of how intricately species interact. Currently, there are some major issues facing endophyte research at the moment. It is still necessary to talk about the mechanisms by which endophytes invade their hosts, including the invasion site and the invasion form (spores, hyphae, etc.). In addition to assisting in the exploration of endophytes' ecological roles, resolving the aforementioned issues will enhance endophytes' potential for application and lay the groundwork for their future growth and application.

REFERENCES:

1. Li Z, Xiong K, Wen W, Li L, Functional endophytes regulating plant secondary metabolism: Current status, Prospects and Applications; International Journal of Molecular Science, 2023, 24 (2), 1153-1158.
2. Aly, A.H., Debbab, A., & Proksch, P. (2011). Fungal endophytes: Unique plant inhabitants with great promises. Applied Microbiology and Biotechnology, 90(6), 1829-1845.
3. Harman, G.E., & Uphoff, N. (2019). Symbiotic root-endophytic soil microbes improve crop productivity and provide environmental benefits. Scientia Horticulturae, 255, 329-337.
4. Strobel, G. A. (2003). Endophytes as sources of bioactive compounds. Microbes and Infection, 5(6), 535-544.
5. Aly AH, Debbab A, Proksch P (June 2011). "Fungal endophytes: unique plant inhabitants with great promises". *Applied Microbiology and Biotechnology*. 90 (6): 1829.

6. Kusari, S., & Spiteller, M. (2012). Metabolomics of endophytic fungi producing associated plant secondary metabolites: progress, challenges, and opportunities. In *Metabolomics in practice* (pp. 65-104). Wiley-VCH Verlag GmbH & Co. KGaA.
7. Kharwar, R. N., Verma, V. C., & Strobel, G. (2011). Diversity and applications of endophytic fungi isolated from medicinal plants. *Microbial Diversity and Biotechnology in Food Security*, 4354.
8. Strobel G, Yang X, Sears J, Kramer R, Sidhu RS, Hess WM (1996) Taxol from *Pestalotiopsis microspora*, an endophytic fungus of *Taxus Wallachian*. *Microbiology* 142:435–440
9. Gurudatt PS, Priti V, Shweta S et al (2010) Attenuation of calprotectin production and negative relation between hyphal biomass and calprotectin content in endophytic fungal strains isolated from *Nothapodytes nimmoniana* Graham (Icacinaeae). *Curr Sci* 98: 1006–1010
10. Kusari S, Lamshoft M, Spiteller M (2009a) *Aspergillus fumigatus* Fresenius, an endophytic fungus from *Juniperus communis* L. Horstmann as a novel source of the anticancer pro-drug deoxy podophyllotoxin. *J Appl Microb*
11. Stierle A, Strobel G, Stierle D (1993) Taxol and taxane production by *Taxomyces cesandreae*, an endophytic fungus of Pacific yew. *Science* 260:214–216
12. Liu K, Ding X, Deng B, Chen W (2009) Isolation and characterization of endophytic taxol-producing fungi from *Taxus chinensis*. *J Ind Microbiol Biotechnol* 36:1171–1177
13. Miao Z, Wang Y, Yu X, Guo B, Tang K (2009) A new endophytic taxane production fungus from *Taxus chinensis*. *Appl Biochem Microbiol* 45:81–86
14. Strobel GA, Hess WM, Li JY, Ford E, Sears J, Sidhu RS, Summerell B (1997) *Pestalotiopsis guepinii*, a taxol-producing endophyte of the Wollemi pine, *Wollemia nobilis*. *Aust J Bot* 45:1073–1082
15. Kumara PM, Zuehlke S, Priti V et al (2012) *Fusarium proliferatum*, an endophytic fungus from *Dysoxylum nectariferum* Hook. f, produces rohitukine, a chromane alkaloid possessing anticancer activity. *Antonie Van Leeuwenhoek* 101:323–329
16. Shi J, Zeng Q, Liu Y (2012) *Alternaria* sp. MG1, a resveratrol-producing Fungus: isolation, identification, and optimal cultivation conditions for resveratrol production. *Appl Microbiol Biotechnol* 95:369–379
17. Tan RX, Zou WX (2001) Endophytes: a rich source of functional metabolites. *Nat Prod Rep* 18:448–459
18. Xiong ZQ, Yang YY, Zhao N, Wang Y (2013) Diversity of endophytic fungi and screening of fungal paclitaxel producer from *Angiojap yew*, *Taxus x media*. *BMC Microbiol* 13:71

19. Eisenreich W, Menhardt B, Hylandst PJ et al (1996) Studies on the bio-Synthesis of taxol: the taxane carbon skeleton is not of mevalonoid Origin. Proc Natl AcadSci U S A 93:6431–6436
20. Xiong ZQ, Yang YY, Zhao N, Wang Y (2013) Diversity of endophytic Fungi and screening of fungal paclitaxel producer from Anglojap Yew, *Taxus x media*. BMC Microbiol 13:71
21. Zhang P, Zhou PP, Yu LJ (2009) An endophytictaxol-producing fungus From *Taxus media*, *Cladosporium cladosporioides* MD2. CurrMicrobiol 59:227–232
22. Staniek A, Woerdenbag HJ, Kayser O (2009) *Taxomycesandreae*: Presumed paclitaxel producer demystified? Planta Med 75:1561–1566
23. Kumaran RS, Kim HJ, Hur BK (2010) Taxol promising fungal endo-Phyte, *Pestalotiopsis* species isolated from *Taxuscuspidata*. J Biosci Bioeng 110:541–546
24. Ruan Q, Patel G, Wang J, Zhou W et al, Current advances of endophytes as a platform for production of anticancer drug camptothecin, Food and Chemical Toxicology, Elsevier, 2021, 151.
25. Yamazaki Y, Urano A, Sudo H, Kitajima M, Takayama H, Yamazaki M, Aimi N, Saito K (2003) Metabolite profiling of alkaloids and Strictosidine synthase activity in camptothecin producing plants. Phytochemistry 62:461–470
26. Fulzele DP, Satdive RK (2005) Comparison of techniques for the Extraction of the anti-cancer drug camptothecin from *Nothapo-Dytes Foetida*. J Chromatogr A 1063:9–13
27. Guerram M, Jiang ZZ, Zhang LY. (2012). Podophyllotoxin, a medicinal agent of plant origin: Past, present and future. Chin J Nat Med 10:161–9
28. Yang X.Z., Shao H., Zhang L.Q., Zhou C., Xuan Q., Yang C.Y. Present Situation of Studies on Resources of Podophyllotoxin. Chin. Tradit. Herb. Drugs. 2001; 32:1042–1044
29. . Canel C, Moraes RM, Dayan FE, Ferreira D. (2000). Podophyllotoxin. 54:115–20
30. Bass C, Puinean AM, Zimmer CT, Denholm I, Field LM, Foster SP, Gutbrod O, Nauen R, Slater R Williamson MS. The Evolution of insecticide resistance in the peach potato aphid, *Myzus persicae*. Insect Biochem Mol Biol. 2014; 51:41-51.
31. Singh N, Singh P, Shrivastva S, et al. (2012). Gastroprotective effect of Anticancer compound rohitukine: Possible role of gastrin antagonism And H(+) K (+)-ATPase inhibition. Naunyn Schmiedebergs Arch Pharmacol 385:277–86.
32. Mohana Kumara P, Sreejayan N, Priti V, Ramesha BT, Rav-Ikanth G, Ganeshaiyah KN, Vasudeva R, John Sant-Hoshkumar TR, Dutt MP, Viswakarma R, Uma Shaanker R (2010) *Dysoxylum binectariferum* Hook.f (Meliaceae), A rich source of rohitukine. Fitoterapia 81:145– 148

33. Byrd JC, Lin TS, Dalton JT, Phelps M, Fischer B, Moran M, Blum K, Rovin B, Colevas AD, Grever MR (2006) Pharmacologically derived schedule of flavopiridol has Significant efficacy in refractory, genetically high risk Chronic lymphocytic leukemia (CLL). *J Clin Oncol* 24:6516
34. H. Yu, L. Zhang, L. Li, C. Zheng, L. Guo, W. Li, P. Sun, L. Qin, *Microbiol. Res.* 165 (2010) 437–449.
35. Kasiotis KM, Pratsinis H, Kletsas D, Haroutounian SA (2013) Resveratrol and related stilbenes: their anti-aging and anti-angiogenic properties. *Food Chem Toxicol* 61:112–120
36. Lee TH, Seo JO, Baek SH, Kim SY (2014) Inhibitory effects of Resveratrol on melanin synthesis in ultraviolet B-induced pigmentation in Guinea pig skin. *Biomol Ther* 22(1):35
37. Kundu JK, Surh YJ (2008) Cancer chemo preventive and therapeutic potential of resveratrol: mechanistic perspectives. *Cancer Lett* 269(2):243–261
38. Lijavetzky D, Almagro L, Belchi-Navarro S, Martínez-Zapater JM, Bru R, Pedreño MA (2008) Synergistic effect of methyl jasmonate and cyclodextrin on stilbene biosynthesis pathway gene Expression and resveratrol production in Monastrell grapevine cell Cultures. *BMC Res Notes* 1(1):132
39. Donnez D, Jeandet P, Clément C, Courot E (2009) Bioproduction Of resveratrol and stilbene derivatives by plant cells and microorganism. *Trends Biotechnol* 27(12):706–713
40. Venugopalan A, Srivastava S (2015) Endophytes as in vitro production platforms of high value plant secondary metabolites. *Bio-technol Adv* 33(6):873–887
41. Kundu JK, Surh YJ (2008) Cancer chemo preventive and therapeutic potential of resveratrol: mechanistic perspectives. *Cancer Lett* 269(2):243–261
42. M. Malgorzata, P. J. Andriena, P., J. Antioxidant Activity of the Main Phenolic Compounds Isolated from Hot Pepper Fruit (*Capsicum annuum* L.), *Agric. Food Chem*, 53, 2005, 1750–1756
43. D. Palevitch, L. E. Cracker, Nutritional and medicinal importance of red pepper (*Capsicum* spp.), *J. Herbs Spices Med. Plants*, 3,1995, 55-83
44. R. Josse, S. S. Sherriffs, A. M. Holowerda, R. Andrews, A. W. Staples, S. M. Philips, Effects of capsinoid ingestion on energy Expenditure and lipid oxidation at rest and during exercise, *Nutr. Metab.*, 7, 65,2010
45. Jones, V.M., Moore, K.A., Peterson, D.M., 2011. Capsaicin 8% topical patch (Qutenza)A review of the evidence. *J. Pain Palliat. Care Pharmacother.* 25, 32–41.
46. Gilbert JA, Neufeld JD. Life in a world without microbes. *PLoS Biol.* 2014;12(12):101-120.

47. George TK, Joy A, Divya K, Jisha MS. In vitro and in silico docking studies of antibacterial compounds derived from endophytic *Penicillium setosum*. *Microb Pathog.* 2019; 131:87–97
48. Archana P, Archana M, Manju S, Madan MG, Girish CU, Raj KL, Ajay KM (2012) Growth and asiaticoside production in multiple Shoot cultures of a medicinal herb, *Centella asiatica*
49. Gilbert JA, Neufeld JD. Life in a world without microbes. *PLoS Biol.* 2014;12(12):e1002020.
50. Porras-Alfaro A, Bayman P. Hidden fungi, emergent properties: endophytes and microbiomes. *Phytopathology* 2011; 49: 291-315
51. Almagro, L.; Fernández-Pérez, F.; Pedreño, M.A. Indole alkaloids from *Catharanthus roseus*: Bioproduction and their effect on human health. *Molecules* 2015, 20, 2973–3000.
52. Kusari S, Zühlke S, Spiteller M (2009) An endophytic fungus from *Camptotheca accuminata* that produces camptothecin and analogues. *J Nat Prod* 72: 2–7 Available:
53. Zhang LR, Wanf J, Son N, Zhang S, Hu J and Kuai J. Exploring novel bioactive Compounds from marine microbes. *Curr. Opin. Microbiol.*, 2006; 8: 276-281.
54. Kaushik B, Chattopadhyay I, Banerjee RK, Bandyopadhyay U. Biological activity and Medicinal properties of neem (*Azadirachta indica*). *Curr. Sci.*, 2002; 82: 1336–1345.
55. Kusari, S.; Verma, V.C.; Lamshoeft, M.; Spiteller, M. An endophytic fungus from *Azadirachta indica* A. Juss. That produces azadirachtin. *World J. Microbiol. Biotechnol.* 2012, 28, 1287–1294
56. Sharma H, Rai AK, Dahiya D et al (2021) Exploring endophytes for In vitro synthesis of bioactive compounds similar to metabolites Produced in vivo by host plants. *AIMS Microbiol* 7:175–199.
57. Santos MLD, Berlitz DL, Wiest SLF et al (2018) Benefits Associated With the Interaction of Endophytic Bacteria and Plants. *Brazilian Archives of Biology and Technology* 61:1–11
58. Daguerre Y, Edel-Hermann V, Steinberg C (2017) Fungal genes and Metabolites associated with the biocontrol of soil-borne plant Pathogenic fungi. In: Mérillon J-M, Ramawat KG (eds) *Fungal Metabolites*. Springer International Publishing, Cham, Switzer-Land, pp 33–104
59. Fadiji AE, Babalola OO (2020) Elucidating mechanisms of endophytes Used in plant protection and other bioactivities with multifunctional prospects. *Front Bioeng Biotechnol* 8:467
60. Bonaterra A, Badosa E, Daranas N et al (2022) Bacteria as biological control agents of plant diseases. *Microorganisms* 10:1759.

61. Kousar R, Naeem M, Jamaludin MI et al (2022) Exploring the anti-Cancer activities of novel bioactive compounds derived from Endophytic fungi: Mechanisms of action, current challenges and Future perspectives. *Am J Cancer Res* 12:2897
62. Leung JC, Cassimeris L (2019) Reorganization of paclitaxel-stabilized Microtubule arrays at mitotic entry: roles of depolymerizing kine-Sins and severing proteins. *Cancer Biol Ther* 20:1337– 1347.
63. Uzor PF, Osadebe PO, Nwodo NJ (2017) Antidiabetic activity of extract and compounds from an endophytic fungus *Nigrospora oryzae*. *Drug Res* 67:308–311.
64. Ezekwesili CN, Ogbunugafor HA (2015) Blood glucose lowering activity of five Nigerian medicinal plants in alloxan-induced diabetic Wistar albino rats. *Anim Res Int* 12:2150–2158
65. Adeleke BS, Babalola OO, Glick BR (2021) Plant growth-promoting Root-colonizing bacterial endophytes. *Rhizosphere* 20:100433.
66. Ferreira MC, Cantrell CL, Wedge DE et al (2017) Antimycobacterial And antimalarial activities of endophytic fungi associated with the ancient and narrowly endemic neotropical plant *Vellozia Gigantea* from Brazil. *Mem Inst Oswaldo Cruz* 112:692–697.
67. Kaushik NK, Murali TS, Sahal D, Suryanarayanan TS (2014) A search for anti-plasmodial metabolites among fungal endophytes of Terrestrial and marine plants of southern India. *Acta Parasitol* 59(4):745–57
68. Farooq T, Hameed A, Rehman K et al (2016) Antiretroviral agents: Looking for the best possible chemotherapeutic options to con-Quer HIV. *Crit Rev Eukaryot Gene Expr* 26:363–381.
69. Raekiansyah M, Mori M, Nonaka K et al (2017) Identification of Novel antiviral of fungus derived brefeldin A against den-Gue viruses. *Trop Med Health* 45:32.

AJPTR is

- Peer-reviewed
- bimonthly
- Rapid publication

Submit your manuscript at: editor@ajptr.com

