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Review Article

Endophytes: A vital source of medicine – A review

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Abstract

Soil and endosymbiotic microorganisms are naturally analogous to plant roots in a symbiotic and non-symbiotic manner. Several groups of plant growth-promoting bacteria and fungi have been identified as bio-fertilizers and isolated microbes have been applied to farmer's agricultural fields to enhance plant biomass and crop productivity. Overall, very few studies have been conducted on the beneficial effect of endophytic microbes on drug production in plants. This review focuses on medicinally valuable plants and their associated endophytic bacteria and fungi to develop drug molecules against human pathogens and other illnesses. Various secondary metabolites, including anticancer, antidiabetic, antibacterial, antifungal, and antiviral compounds, are present in both endophytes and their host plants. The number of secondary metabolites produced by fungal endophytes and their host plants is reported to be greater than that of endophytic bacterial species. The current proficiency of endophytic bacterial and fungal metabolites and their bioactivity against diseases are addressed in this review.

Keywords: *Bioactive metabolites, Endophytic bacteria, Endophytic fungi, Medicinal plants, Pathogens*

INTRODUCTION

Endophytes are microorganisms that live in intracellular locations in the plant body without causing damage to the plant. These bacteria and fungi produce a wide range of secondary metabolites that are helpful in producing drug molecules. Humans suffer due to various diseases caused by pathogenic bacteria, fungi, viruses, and other illnesses. The mortality rate of humans was reduced after the 20th century because of the use of antibiotics and drugs in animals, which are consumed by us [1]. Although several drugs are available to cure diseases, some of them are not effective, and the development of antibiotic resistance leads to the need to identify new drugs to control pathogens.

Medicinal plants and their associated endophytes are a valuable source of crucial secondary metabolites and bioactive compounds that provide more than 80 % of the natural drugs available in the market [2]. Treatment with synthetic drugs may cause side effects; thus, low-risk therapies using traditional approaches, including synthetic drugs, herbal remedies, and biological drugs, are useful in curing diseases and illnesses [3]. Plant and microbial secondary metabolites are viable sources for producing new antibiotics and drugs for treating diseases and disorders. The present review focuses on the importance of several endophytic bacteria and fungi and their host plants' secondary metabolites for various biological effects in humans.

Endophytic bacteria

Several bacterial species living inside plant tissues depend on host plants for their survival with mutual benefits [4]. Endophytic bacteria inhibit the growth of human and plant pathogens, and their symbiotic association is beneficial to the host [5]. Endophytes produce several metabolites that are relatively similar to host plants, and the chemistry and biosynthesis of the compounds and their derivatives are also similar. The bioactivity of endophyte-produced compounds is higher than that of the respective host metabolites. Various groups of economically important secondary metabolites have been identified and recognized in endophytes [6]. Studies of endophytic bacteria and host plant associations and their active metabolite production are very limited [7]. The crosstalk between interspecies microorganisms and the similar ecological habitats of both endophytes and hosts is a reason to produce structurally similar natural compounds [6]. The utilization of natural endophytic agents to produce economically valuable compounds for pharmaceutical purposes has some advantages, including a lower production cost [8].

Antibiotics, including antifungal and antibacterial metabolites from endophytes, are considered novel sources of antibiotic production [9]. Some of the endophytes belonging to actinomycetes act as anti-diabetic agents [10]. Organic compounds, such as alkaloids, flavonoids, tannins, terpenoids, steroids, phenolic acids, chinones, quinones, and xanthones, synthesized in plants, bacteria, and fungi are considered secondary metabolites because they are not essential for their growth but protect against biotic competition and enable tolerance to adverse environmental conditions [11].

Drugs from medicinal plants and their endophytic bacteria

Medicinally valuable compounds present in plants are considered some of the most important sources of drugs used to treat human illnesses [12] (Table 1). Herbal drugs are gaining global attention due to their effective and negligible side effects. Indians use healthcare products derived from medicinal plants through homeopathic treatments [13]. Chinese have used the perennial herb *Pinellia ternata* (Thunb.) Berit., in traditional medicine for more than 2000 years [14], because it contains purine alkaloids [15], and it is used as an anti-emetic, analgesic, and sedative [14]. Another traditional bulbous plant, *Crinum macowanii* Baker, has been used to treat several ailments, including venereal disease, inflamed sores, itchy rashes, acne, backache, boils, swellings of the body, and urinary tract problems. It is also beneficial for increasing lactation in cows and women [16]. *Crinum macowanii* bulb extracts prevent infection by common pathogenic bacteria [17]. In addition, cytotoxic activity compounds (crinamine, bulbispermine, and lycorine) prevent human oral epidermoid carcinoma KB cells, apoptosis-resistant cells, and BLS mouse melanoma cells [16]. The essential oil extracted from the leaves of *Guatteria australis* prevents *Staphylococcus aureus* and *E. coli* infections due to the principal antibacterial sesquiterpene compound, germacrene, present in the essential oil [18].

Some medicinal plants and their inhabiting bacteria show similar pharmacological activity. For example, *Tridax procumbens* L is known to heal wounds and has antimicrobial activity potential, and their endophytic bacteria also confer similar wound-healing properties and produce novel antibiotics [9]. Some *Bacillus spp.* (*B. amyloliquefaciens*, *B. indicus*, *B. pumilus*, *B. subtilis*), *Pantoea* (*P. agglomerans and P. stewartii*) and, *Pseudomonas spp.* (*P. oryzihabitans* and *P. psychrotolerans*) can synthesize diverse groups of economically important secondary metabolites [43].

Herbal diabetic medicines have been reported to attract diabetic patients to synthetic chemical pills because they are less expensive and have no side effects [44]. Actinomycetes isolated from the stems and leaves of *Leucas ciliata* and *Rauwolfia densiflora* have been helpful in treating diabetes [10]. The new ergosterol derivative (23R-hydroxy-(20Z,24R)-ergosta-4,6,8(14),20(22)-tetraen-3one) and its related compound (22E,24R)-ergosta-4,6,8(14),22-tetraen-3-one) secreted from the endophytic bacterium *Bacillus wiedmannii* exert several biological effects [6]. The endophytes isolated from *Pinellia ternata* increase the yield of the host plant and stimulate the synthesis of new alkaloids [15].

Table 1: Bioactivity of endophytes residing in medicinal plants

Medicinal plant	Biological activity	Reference
Polygonum chinense (L.)	Antimicrobial and antioxidant activity	[8]
Tridax procumbens (L.)	Antimicrobial activity and wound healing activity	[9]
Leucas ciliata *(Benth.) and* Rauwolfia densiflora *(Wall.)*	Treat the diabetes	[10]
Pinellia ternata (Thunb.) Berit.	Purine alkaloids – anti-emetic, analgesic, and sedative used as anticancer, painkiller, and sleep disorders	[14,15]
Crinum macowanii (Baker.)	Treated venereal disease, inflamed sores, itchy rashes, acne, backache, boils, swellings	[16]
Crinum macowanii (Baker.)	Anticancer and antibacterial potential	[17]
Guatteria australis (A. ST.-HIL)	Antibacterial Activity	[18]
Catharanthus roseus (L.) and *Boscia variabilis* (Coll. & Hemsl)	Prevention of infection by human pathogenic bacteria and plant pathogenic fungi	[19]
Calotropis procera (Aiton)	Antimicrobial activity	[20]
Aralia nudicaulis (L.)	Prevent pathogenic bacterial and fungal growth	[21]
Pinellia ternata (Thunb.) Berit.	Anti-inflammation activity, anticancer, anti-anxiety	[22]
Anoectochilus roxburghii (Wall.)	Reducing autoimmune hepatitis	[23]
Baliospermum montanum (Willd.)	Treatment of asthma, constipation, and jaundice	[24]
Bauhinia forficate (Link.)	Antibacterial activity	[25]
Coccinia grandis (L.)	Antidiabetic activity	[26]
Solanum xanthocarpum *(L.)*	Suppresses leukemic and tumor cell growth	[27]
Withania somnifera (L.)	Anti-inflammatory activity	[28]
Artemisia argyi (H.Lev.&Vaniot)	Anti-inflammatory activity	[29]
Nothapodytes foetida (Wt.)	Chemotherapeutic agent	[30]
Cardiospermum helicacabum (L.)	Used for treating ophthalmodynia and arthritis	[31]
Arnica montana (L.)	Reduce the fungal and viral infections	[32]
Arisaema erubescens (Wall.)	cytotoxic activity	[33]
Adiantum philippense (L.)	Antimicrobial activity	[34]
Euphorbia prostrate (Aiton)	Antibacterial and antiproliferative activities	[35]
	Antioxidant potential	[35]
Trigonella foenum-graecum (L.)		
Dysosma versipellis (Hence) M.Cheng	Antimicrobial and anticancer activity	[36]
Lycoris aurea (L'Hér.) Herb.	Antifungal activity against human fungal pathogens	[37]
Solanum mauritianum (Scop.)	Antibacterial activity	[38]
Moringa oleifera (Lam).	Antifungal activity	[39]
Ginkgo biloba (L.)	Anticancer and antioxidant activity	[40]
Gongronema latifolium *(Benth.)*	Anti-inflammatory activity	[41]
Panax notoginseng (Burkill.)	Inhibitory effects against nitric acid production on murine macrophage cell line	[42]

Antimicrobial effects of endophytic bacteria

The endophytes isolated from *Catharanthus roseus* and *Boscia variabilis* Collett & Hems not only prevent the growth of human pathogenic bacteria but also prevent plant pathogenic fungi [19]. Infection by common pathogens, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus agalactiae*, *Salmonella typhi*, *Serratia marcescens*, and *Staphylococcus aureus*, is controlled by extracts that contain large quantities of tannins, flavonoids, saponins, and phenolics produced by *Bacillus siamensis* and its host plant, *Calotropis procera* [20]. The growth of various pathogenic bacteria is suppressed by extracts obtained from several endophytic bacteria, such as *Acinetobacter guillouiae*, *Pseudomonas moraviensis*, *Pseudomonas sp*., *Rahnellaaquatilis*, *Bacillus cereus*, *Novosphingobium sp*., *Raoultella ornithinolytica*, and *Burkholderia tropica* [17].

Several reports suggest that endophytic bacteria have the potential for antibacterial, antifungal, and cytotoxic properties due to the production of alkaloids, steroids, terpenoids, flavonoids, and peptides [7] (Figure 1 and Table 2). The culture extract of *Coniothyrium sp*. which resides in the rhizomes of *Aralia nudicaulis*, contains palitantin, botrallin, craterellin C, mycosporulone, spiromassaritone, and massarigenin D, which prevents the pathogenic bacteria and fungal growth [21]. Novel antibiotics produced from microorganisms could be an alternative method for reducing antibiotic resistance and preventing pathogen growth [47].

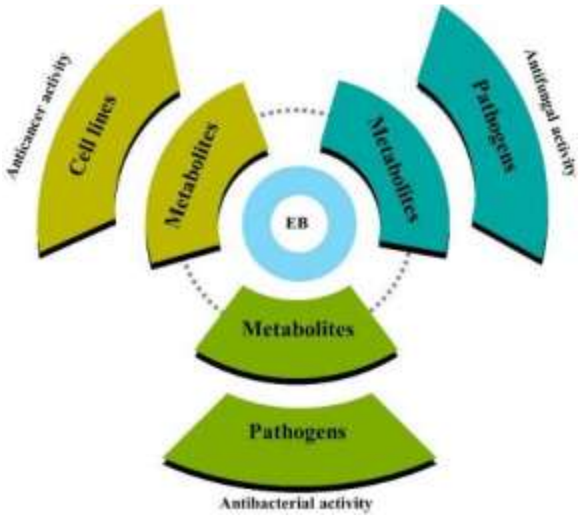

Figure 1: Endophytic bacteria (EB) secrete metabolites and their biomedical activities

Anticancer, anti-inflammatory, and antioxidant effects of endophytic bacteria

Plant-based alkaloids, brassinosteroids, and taxols play vital roles in preventing cancer cell growth, and their therapeutic applications are well established [30]. The endophytic bacteria *Pinellia ternata* shows anti-inflammation, anticancer, and anti-anxiety activity [22]. Anti-cancer and antiviral compounds are present in a diverse group of organisms. For example, guanosine is present in medicinal plants, [48] and inosine is present in animals and microorganisms [49]; both are reported as effectively controlling cancer and viral growth. In some cases, *B. thuringiensis* and *B. licheniformis* secrete guanosine which prevents cancer [15]. The amine compounds extracted from *Acinetobacter* sp. have an antitumor effect against oral squamous carcinoma cells [46]. In addition, the *C. macowanii* bulbs that reside in the endophytic bacterial extract have anticancer and antibacterial potential [17].

Endophytic fungi

Fungi colonize various tissues of plants without causing any negative effects; these are considered endophytic fungi. These fungi secrete antibacterial, antifungal, antiviral, insecticidal, antidiabetic, antioxidants, and anticancer compounds, along with plant-growth regulating chemicals (Figure 2) [50]. Fungi have been integrated with several plants for 400 million years in nature by regulating the physiological process to enhance plant growth and tolerate the abiotic and biotic stress in the environments of the host plants [34]. Diversified endophytic fungi have been identified in several plants [24], and their primary and secondary bioactive compounds are beneficial to host plants and have the potential to be pharmaceutically valuable drugs against animals and human diseases [23,38,41]. Fungal alkaloids, flavonoids, phenols, benzopyranones, quinines, and quinones act as valuable drugs [51], and the structure and function of other bioactive products are also important for preparing drugs [52].

Table 2: Bioactivity of endophytic bacteria

Endophytic bacteria	Biological activity	Reference
Bacillus wiedmannii	Antibacterial efficiency	[6]
B. thuringiensis and *B. licheniformis*	Anticancer activity	[15]
Acinetobacter guillouiae, *Pseudomonas moraviensis*, *Rahnellaa quatilis*, *Bacillus cereus*, *Novosphingobium* spp., and *Raoultella ornithinolytica*	Inhibit the bacterial pathogenic activity	[17]
Bacillus siamensis	Antimicrobial activity	[20]
Coniothyrium spp.	Suppress the pathogenic bacterial and fungal growth	[21]
Burkholderia gladioli	Inhibitory effect against azole antifungal-resistant mutants of *A. fumigatus*.	[37]
Bacillus spp. (*B. amyloliquefaciens*, *B. indicus*, *B. pumilus*, and *B. subtilis*), *Pseudomonas spp.* (*P. oryzihabitans* and *P. psychrotolerans*), and *Pantoea spp* (*P. agglomerans* and *P. stewartii*)	Produce economically important secondary metabolites	[43,45]
Acinetobacter spp.	Anti-tumor activity	[46]

In addition, fungi-secreted amylase, cellulose, lipase, protease, laccase, and protease are useful for textiles, food processing, detergents, pharmaceuticals, and agrochemical applications [24].

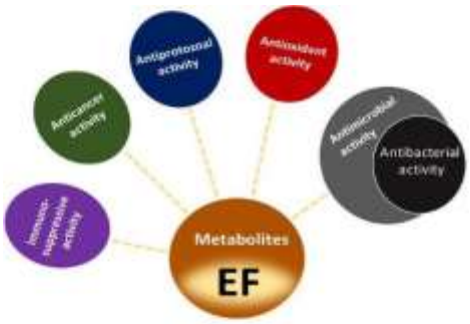

Figure 2: Endophytic fungi (EF) secrete metabolites and their biomedical activities

Drugs from medicinal plants and their endophytic fungi

The various bioactive metabolites present in medicinal plants are resources of the cosmetic and pharmaceutical industries. The endophytes residing in plants are a good source of novel bioactive compounds, such as several alkaloids, flavonoids, terpenes, and organic acids which are involved in antiviral, antidiabetic, antilipemic, anti-inflammatory, and immunomodulatory properties (Table 3). The endophytes associated with *Anoectochilus roxburghii*, edible, and medicinal plants produce kinsenoside as an immunosuppressive compound for reducing autoimmune hepatitis [23].

Similarly, endophytic fungi have been found on medicinal plant *Baliospermum montanum* (Willd.) Muell. Arg, which is utilized to treat asthma, constipation, and jaundice [24]. Some fungi, i.e *Trichoderma* spp., *Acremonium* spp., *Rhizoctonia* spp., *Fusarium* spp., and *Alternaria* spp., colonized medicinal orchids (*Dendrobium* spp. [53]. Another study reported [25] that *Aspergillus ochraceus*, *Trichoderma piluliferum*, *Acremonium curvulum*, *Gibberella fujikuroi*, and *Myrothecium verrucaria* are present in the medicinal plant, *Bauhinia forficate*, which shows strong antibacterial activity against *Staphylococcus aureus*. The endophytic fungus, *Nigrospora oryzae* which resides in *Coccinia grandis* leaves is used to treat diabetes [26]. Pelo *et al*, [38] identified *Collectotrichum boninense, Cladosporium* spp., *Aureobasidium pullulans*, *Penicillium chrysogenum*, *Fusarium* spp., *Hyalodendriella* spp*., Paracamaros porium leucadendri,* and *Talaromyces* spp., from the leaves of *Solanum mauritianum*.

Zingiber officinale, *Alpinia galanga*, *Curcuma longa*, *Hedychium coronarium*, and *Curcuma amada* plants harbor endophytic fungus *Talaromyces pinophilus* which secretes nutritional and non-nutritional factors, such as the enzyme L-asparaginase [54]. *Phomopsis vexans* residing in *Solanum xanthocarpum* produces lovastatin, which lowers blood cholesterol, and isoprenoids, which suppress leukemic and tumor cell growth [27]. *Taleromyces pinophilus* present in the *Withania somnifera* leaves produces withanolides [27]. *Artemisia argyi* H. Lév., and Vaniot and their endophytes are helpful in treating bruising, jaundice, amenorrhea, malaria, dysmenorrhea, metrorrhagia, and inflammation by secreting polyketides, polysaccharides, terpenes, and flavonoids [29]. Endophytes in *Nothapodytes foetida* are a source of camptothecin [30]. *Cardiospermum helicacabum* L. is useful in curing ophthalmodynia, arthritis, strangury, fever, amenorrhoea, lumbago, and neuropathy, and endophyte *Pestalotiopsis pauciseta* syntheses taxol [31], which has been widely used for the treatment of a variety of cancers. *Aspergillus brasiliensis* and *Fusarium oxysporum* isolated from *Baliospermum montanum* plants synthesize the bioactive compound 1,3,5-trioxane, and two other fungi, *Trichoderma reesei,* and *Aspergillus brasiliensis* produce methenamine and N-hydroxy-N-methyl [24], respectively.

Antimicrobial activity of endophytic fungi

Pestalotiopsis spp. synthesizes alkaloids, terpenoids, coumarins, chromones, quinones, semiquinone peptides, xanthones, phenols, and other structural compounds, including pestacin, isopestacin, and ambuic acid, which express antagonistic activity against *Pythium ultimum* [40]. Toxoflavin-producing *B. gladioli* control *Aspergillus fumigatus* infections in humans [37]. *Corynespora*, *Endomelanconiopsis*, and *Thozetella* strains also show antifungal and antibacterial activity [55]. *Streptomyces* present in *Arnica montana* secretes bioactive metabolites, including cycloheximide, which is useful for reducing fungal and viral infections [32]. *Phoma* spp. from *Arisaema erubescens* plants produces cercosporamide, which has as cytotoxic activity, and the a-tetralone derivative (3S)-3, 6, 7-trihydroxy-a-tetralone [33] causes growth inhibition of *Fusarium oxysporium* and *Rhizoctonia solai*. Flavasperone synthesis from *Aspergillus niger* which has antimicrobial activity, and aurasperone A, a dimeric naphtho-pyrone synthesized from *Aspergillus awamori* [56], prevent Taq DNA polymerase activity.

Table 3: Bioactivities of endophytic fungi

Endophytic fungus	Biological activity	Reference
Fusarium chlamydosporum	Antimicrobial and antioxidant activity	[8]
Coniothyrium spp. and *Coniothyrium palmarum*	Preventing pathogenic bacterial and fungal growth	[21]
Aspergillus versicolor	Immunosuppressive activity	[23]
Aspergillus brasiliensis and *Trichoderma reesei*	Explored for development of novel drugs with commercial values	[24]
Aspergillus ochraceus, *Trichoderma piluliferum*, *Acremonium curvulum*, *Gibberella fujikuroi*, and *Myrothecium verrucaria*	Antibacterial activity	[25]
Nigrospora oryzae	Antidiabetic activity	[26]
Phomopsis vexans	Suppresses leukemic and tumor cell growth	[27]
Talaromyces pinophilus	Anti-inflammatory activity	[28]
Pestalotiopsis pauciseta	Anticancer activity	[31]
Nigrospora sphaerica	Antimicrobial activity	[34]
Byssochlamys spectabilis and *Alternaria* spp.	Antibacterial and antiproliferative activities	[35]
Alternaria spp.	Antioxidant potential	[35]
Curvularia spp.	Antimicrobial, and antioxidant activities	[35,59]
Talaromyces spp. *Fusarium solani, Taxomyces andreanae*, *F. oxysporum*	Drug synthesis in pharma industries, Anticancer activity	[38]
Aureobasidium pullulans	Antimicrobial, immuno-modulatory, anti-tumor activity	[38]
Nigrospora spp.	Antifungal activity	[39]
Colletotrichum spp.	Anticancer and antioxidant activity	[40]
Pestalotiopsis spp.	Antagonistic activity	[40]
Corynespora cassicola	Anti-inflammatory activity	[41]
Fusarium tricinctum	Inhibitory effects against nitric acid production on murine macrophage cell line	[42]
Beauveria bassiana and *Fusarium* spp.	Apoptotic and cytotoxic effects	[50]
Talaromyces pinophilus	Secretes nutritional and non-nutritional factors	[54]
Corynespora and *Endomelanconiopsis*	Antifungal and antibacterial activity	[55]
Aspergillus niger and *Aspergillus awamori*	Antimicrobial and antibacterial activity	[56]
Aspergillus fumigatus	Antifungal, antibacterial, and antitumor activity	[57]
Acremonium citrinum	Antimicrobial and cytotoxic activity	[58]
Purpureocillium lilacinum	Antiprotozoal activity	[59]
Aspergillus fumigatus	Anticancer activity	[60]

The diversified and rich sources of alkaloids, flavonoids, steroids, terpenoids, cyclopeptides, and anthraquinones are found in endophytic fungi and show their antimicrobial activity [37]. The endophytic fungus *Nigrospora sphaerica* isolated from *Adiantum philippense* produces antimicrobial compounds, such as phomalactone which controls the growth of human and plant pathogens [34]. *Byssochlamys spectabilis* and *Alternaria* spp. associated with *Euphorbia prostrate* have antibacterial and antiproliferative activities [35]. In addition, *Dysosma versipellis* produces a novel antimicrobial and anticancer compound, podophyllotoxin [36]. *Solanum mauritianum* resides in a number of endophytic fungi that effectively control *Mycobacterium tuberculosis*. Similarly, anthraquinone isolated from *Talaromyces* spp. and penicillic acid from *Fusarium solani* and other fungal endophytes are more significant for preparing drugs in the pharmaceutical industry [38]. Endophytic fungi *Nigrospora* spp. present in *Moringa oleifera* produce dechlorogriseofulvin, griseofulvin, mullein, and 8-dihydroramulosin, which act as antifungal agents [39].

Secondary metabolites tryprostatin C, gliotoxin, fumagillin, bis(methylthio)gliotoxin, fumiquinazoline, pseurotin A, pseurotin D, and pseurotin F2 produced from *A. fumigatus* have antifungal, antibacterial, and antitumor activity [57]. *Nigrospora sphaerica* synthesizes new antimicrobial bioactive compounds, such as diketopiperazines, nigrosporolides, epoxydons nigrosporolides, nigrosporins, pyrones lactones, and diterpenes [34]. *Acremonium citrinum* has been found in *Fructus mori* and synthesizes acrepyrone A and sorbicillinoids including trichodimerol, dihydrotrichodimerol, and tetrahydrotrichodimerol. It produces various bioactive metabolites [58] that show antimicrobial and cytotoxic activity. *Curvularia* spp., producing curvulamine, curindolizine, apralactone A, curvulide A, cochliomycin A, cynodontin, 2'-deoxyribolactone, hexylitaconic acid, ergosterol, lunatin, and zaragozic acid A [35,59], show antimicrobial and antioxidant activities.

Anticancer, anti-inflammatory, and antioxidant activity of endophytic fungi

An anticancer drug, taxol was initially produced from the plant *Taxus brevifolia*, and later their endophytic fungi were shown to produce the same metabolites in larger quantities through industrial production. Taxol synthesized from *Taxomyces andreanae,* camptothecin from producing *Fusarium solani*, and vinblastine and vincristine isolated from *Fusarium oxysporum* has various biological activities [38]. The endophytic fungus *A. fumigatus* synthesizes a novel anticancer drug, deoxypodophyllotoxin [60], and similarly, *Aureobasidium pullulans* secretes β-(1 → 3, 1 → 6)-glucans, which are involved in antimicrobial, immunomodulatory, anti-tumor, fungicide, and food allergy inhibition activities [38]. *Colletotrichum* spp., residing in *Ginkgo biloba* secretes flavones to control cancer and has antioxidant activity [40]. However, Das *et al*, [8] reported that the phenolic compounds produced by endophyte *F. Chlamydosporum* and plant *Polygonum chinense* show antimicrobial and antioxidant properties.

Beauvericin *from Beauveria bassiana* and *Fusarium* spp. plays a vital role in controlling blowflies, Colorado potato beetles, and mosquito larvae and also shows apoptotic and cytotoxic effects [50]. Antiprotozoal activity against *Leishmania donovani* due to the presence of purpureone and an ergochrome moiety was recorded in the endophytic fungus *Purpureocilliumli lacinum* [59]. The anti-inflammatory compounds of depsidones and diaryl ether derivatives have been synthesized from *Corynespora cassicola* isolated from *Gongronema latifolium* [41]. *A*. *versicolor* is an endophytic fungus that produces isochromane lactones, benzolactones, versicobenzos A and B, versicoisochromanes A and B, asperfuran A, furancarboxylic derivates, ergosterol-type steroids, and asperergoster A [23]. These compounds have immunosuppressive activity. *Alternaria* spp. isolated from *Trigonella foenum-graecum* show antioxidant potential [35]. Alkaloids, such as rigidiusculamide E and (-(a-oxyisohexanoyl-N-methyl-leucyl)2-), secreted from *Fusarium tricinctum* residing in *P. notoginseng* roots [42], have inhibitory effects against nitric acid production on the murine macrophage cell line.

CONCLUSION

Medicinal plants are used in specific treatments. Some medicinal plants are rarely cultivated in nature, but they contain more bioactive materials. The present review suggests that isolation, identification, and mass culture of viable drug molecules producing endophytes is a vital source of medicine and saves medicinal plants.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Selvaraj Perumal, Ramalingam Radhakrishnan, and Ramaraj Sathasivam wrote the first draft of the review. Ramalingam Radhakrishnan and Sang

Un Park conceptualized and contributed the idea and outline of the review. Ramalingam Radhakrishnan and Ramaraj Sathasivam prepared the figures. Ramalingam Radhakrishnan, Muthukrishnan Arun, and Sang Un Park proofread and edited the draft. All authors approved the review for publication.

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