Endophytic microorganisms in traditional medicinal plants -A Review

NishaRaj S

SAS SNDP Yogam College, Konni, Pathanamthitta
(Affiliated to Mahathma Gandhi University, Kottaym)
Corresponding author-NishaRaj S
nishsek@yahoo.co.in

Abstract

Medicinal plant associated microorganisms or endophytic microbes are ubiquitous in nature and confer high therapeutic value. They live inside plants as they find the location was highly constant as compared to soil where the plant develops. Few of them are found to be present in host plants for a part of their lifecycle. They are involved in antagonism, mutualism and parasitism and show complex host-microbe relationship. The endophytic organisms that possess larger genomes with specific genes make them adapt to different environments while those with smaller genomes exist in a stable environment. The endophytes helps the host plant in tolerating stress (biotic and abiotic), improve insect and pest resistance, storage of nutrients and growth. Endophytes are well known in production of natural biologically active compounds such as drugs, enzymes and hormones. Therefore, these organisms are explored for discovery of novel drugs that could be used in health care.

Keywords: medicinal plants, endophytic bacteria, endophytic fungi, endophytic actinomycetes.

Introduction

Endophytes are microorganisms (bacteria or fungi or actinomycetes) present in living tissues of autotrophs (intercellular or intracellular) without causing any damage to host plants. They form saprophytic relationship with hosts and sometimes pathogenic when the host plant is stressed. Both the microorganism and the host balance each other by some herbicidal products and anti-microbial metabolites synthesized by the plant (Wilson, 1995). The endophytes establish obligate or facultative relationship with the plants. They are well known producers of bioactive compounds but less explored (Carroll, 1988). These compounds are also helpful in protecting the plants from environmental changes, disease causing agents, abiotic stress, herbivores and habitat changes. The bioactive compounds produced by these endophytes possess high economic value as it produces antibiotics, drugs and ingredients necessary for food industry. They are also helpful in recycling of nutrients, biodegradation and bioremediation. These microbes are known to produce growth regulating substances thereby enhancing the nutrient intake directly improving biomass and yield of grains (Chadha et al., 2014; Ghimire and Carven, 2011).

The endophytes were found to be present in various parts of host plants and so isolating them is quite difficult (Hallmann et al., 1997). The parts where endophytes are present are meristem, primordial, resin ducts, roots, bark, stem, buds, midrib, leaf segments and leaf blade (Abdel-Azeem et al., 2016). Different methods have been reviewed for the isolation of endophytes from a internal as well as surface-disinfected plant tissue.

Novel natural lead compounds may be isolated by improving resources of endophytes. These compounds may then be subjected to chemical synthesis for mass manufacturing. Though several studies have been performed in recent years about colonization pattern and effects, better understanding about these organisms, host plants, their applications, ecology and biology of host plants is necessary (Akpotu et al., 2017). This review is therefore focused on plants hosting endophytic microorganisms, types of microbes, their specificity, beneficial effects of host plants acquired by the symbiotic relationship of endophytes and therapeutic applications of host plants as well as endophytic microorganisms.

Types of endophytes

The endophytes (bacteria and fungi) were associated with wide range of plant varieties in different ways. The bacterial strains of endophytes are diverse in environment and are responsible for the production of various biologically active compounds and the compounds possess antimicrobial and antitumor activity, where most of them are reported from the species, *Streptomyces* (Berdy, 2012). Fungi are heterotrophic group of organisms with various life cycles that include symbiotic relationships with a wide variety of autotrophic organisms (Saar et al., 2001). Studies have proved the presence of endophytic fungi in many medicinal herbs and it is reported that they live in majority in non-grass plants.

Bacterial endophytes

Bacteria are omnipresent and are found in all environments though their association pattern and applications vary with the host and are not yet deeply understood. Almost all plants including medicinal plants inhabit different species of microbes which may be termed as plant endomicrobiome . They play a vital role in improvement of plant metabolism, nutrient uptake and overall growth and fitness (Hardoim et al., 2015).Both Gram positive and negative bacteria belonging to classes α, β, γ-proteobacteria and actinobacteria were isolated from medicinal plants. They are beneficial to host plants in nitrogen assimilation, phosphate solubilization, growth promotion and regulation (Liu et al., 2016). They are also responsible for regulation of producing biological components (Qin et al., 2016). Endophytic microorganisms isolated from medicinal plants have been identified as an important source of new antimicrobial compounds (Wicaksono et al., 2016).

The endosymbiotic bacteria are reported to improve absorption of nutrients thereby having a direct impact on growth of host plant (Shi et al., 2014). The bacteria, when colonizes, is believed to move from internal space of host to the surface (Hallman et al., 1997). But still, no report gives a clear explanation on the perseverance of survival of microbes inside plant tissues. Most viable and competitive organisms are able to migrate between different tissues of host or different locations on same tissue inside the plant (Maropola et al., 2015). The diversity of bacterial species is influenced based on climate, soil type, geographical conditions, ecological interactions, anthropogenic activities and natural disasters .Around 200 genus of bacterial strains are identified as endophytes, in which majority of genus grouped under Actinobacteria, Proteobacteria, and Firmicutes (Golinska et al., 2015). The endophytic bacterial species may be gram-positive or gram-negative eg. *Achromobacter*, *Acinetobacter*, *Agrobacterium*, *Bacillus*, *Pseudomonas*, *Xanthomonas* etc. (Sun et al., 2013).

Fungi

Many studies proved the presence of endophytic fungus in medically important herbs. Fungal endophytic microorganisms are of two main groups. 1. Fungi that colonize in diverse range of plants 2. Specific fungi living in some monocot plants (Wani et al., 2015).Almost all plants possess some endophytic association with fungal species belonging to phylum Glomeromycota, Ascomycota, Basidiomycota and Zygomycota (Zeilinger et al., 2016) of genus*Cephalosporium, Chaetomium, Cladosporiaceae, Coelomycetous, Sordariomycetes, Botryosphaeriaceae, and Hypocreaceae*.Around 100 species of plants wereidentified as hostsof endophytic fungalstrains (Newman and Cragg, 2015). Bhagobaty and Joshi (2011) reported 705 fungal endophytes that are capable of producing active biological compounds from 5 traditional medicines.

However, fungal surveys conducted during the last 30 years have demonstrated that tissues of the vast majority of nongrass plants are colonized by endophyticmicrofungi . The organisms are found to be present in tissues of branches, fruits, flowers, bark, seeds, roots, twigs, stems etc. of the hosting plant species. Non-grass hosts are generally high, more diverse and endophytic fungi are found abundantly in their tissues . Such, endophytes are horizontally transmitted from plant to plant. They assemble in specific part that is entirely different from other tissues of the same plant (Zhang et al., 2012). The assembling of fungi in fruits and flowers are entirely different as they are young and develop fast . The distribution of endophytic microfungi on the basis of geographical location, ecology and hosts are less studied (Venugopalan et al., 2015).

Fungal endophytes studied to date have been isolated based on culture-dependent methods and identified by characterization of physiological factors and molecular approaches . The knowledge of infection due to fungal endophytes, their diversity and taxonomy are still unknown as the knowledge of unculturable endophytes is limited. To overcome this, culture-free methods like 16S rRNA gene sequencing and RFLP were preferred to study taxonomy, diversity and host-fungi interaction. Hence, the strains that grow slowly in a media which might get lost during culturing may also be studied for their potency .

Actinomycetes

Actinomycetes belong to the phylum Actinobacteria and form spores and mycelia as in fungal species. For this reason, they were considered as an intermediary form of bacteria and fungi (Chaudhary et al., 2013; Barka et al., 2016).Actinomycetes live in the innermost tissues of healthy hosts and they are important sources of new biologically active components (Gohain et al., 2015). Medicinal plants, crops, halophytes and woody trees are all sources of endophytes .Many researchers focus on therapeutical utility of actinomycetes from traditionally known medicinal plants (Nalini and Prakash, 2017). Previous reports have proved that actinomycetes strains are the prime source of new anticancer, anti-inflammatory, anti-microbial and growth promoting agents (Viaene et al., 2016; Matsumoto and Takahashi, 2017). Endophytes present in plants living in less explored environments have been studied by many researchers in recent years (Hokama et al., 2016; Peña et al., 2016; Tonial et al., 2017).

The endophytic actinobacteria were linked with the host plant at its early stage of development. Most of the bacteria were isolated from the roots of the plants, while stems and leaves contain very low quantity of actinobacteria (Golinska et al. 2015). Some actinobacteria were present in stomata of the plant. Comparedto other plant types, woody plants havelargevariety of actinobacteria, as they are natural inhabitant of soil that easily come in connect with plant roots (Maheshwari 2017).

Specfic potent actinobacterial community found in medicinal plants such as *Ainsliaea henryi, Dioscorea opposite, Potentilla discolor, Rhizoma arisaematis, Ophiopogon japonicas* etc. were reported with anti-tumour and anti-microbial effects (Jia et al., 2016). Endophytic *Streptomyces* are genus that forms a unique source of new antibiotics .

Table 1. Benefits of endophytic organisms and their host plants.

Medicinal plants	Endophytic organism	Beneficial effects	References
Aucuba japonica	*Streptomyces* sp. TP-A0556	AntibioticactivityagainstGram-positiveand-negativebacteria	Liu et al., 2017
Azadirachta	*Pestalotiopsis*sp.	Exhibited maximum radical	Li et al., 2017

indica		scavengingactivity,antihypertensive, Antibacterial	
Allium fistulosum	*Streptomyces*sp.	Antifungalactivity,Streptomycesproducesnovobiocinasamajor metabolite having antimicrobial activity	Maggini et al. (2017)
Garcinia atroviridi	*Botryosphaeria*sp.	Antimicrobialactivity	Gangwar et al. (2017)
Costusspeciosus	*Bipolaris sorokiniana*	Toxicity againstbrine shrimps	Qader etal. (2017)
Vochysia divergens	*Aeromicrobium ponti* LGMB491	Antibacterial activity	Gos et al., (2017)
Alpinia galanga	*Streptomyces* sp.Tc022	Very strong antibacterial andantifungalactivities	Sufaati(2016)
Artemisia annua L	*Bacilluscereus*	Antioxidant, preventingDNAdamage	Roy et al., 2015
Berberislycium	*Pseudomonas putida*	Antimicrobialactivity	Sheoran etal. (2015)
Cistanches deserticola	*Penicillium chrysogenum*	Neurocyte protection effectagainst oxidative stress-induced cell death in SH-SY5Ycells having activities in preventing and treating cranial nerve diseases	Samaga and Rai(2015)
Gymnema sylvestre	*Penicillium oxalicum*	Antidiabetic agent, endophytic fungi isolated from G. Sylvestre, produced gymnemagenin	Deshmukh Sunil et al. (2015)
Ricinus communis	*Alternaria*sp.	Acetylcholinesterae (ache) inhibitor, potentinsecticidalactivity	Parthasarathy and Sathiyabama (2014)

Medicinal Plants as Host

All plants are associated with microbes and these microorganisms are responsible for quality, health and nutrition of medicinal plants (Mendes et al., 2011; 2013).The rhizosphere can host up to 10^{11} microbial cells per gram root with more than 30,000 different prokaryotic species (Berendsen et al., 2012). Each plant species harbors a specific rhizosphere microbiome dependent of the present soil community (Nath et al., 2015).The diversity of this microbiome depends on type of soil, climatic changes, health and developmental stages of host, pesticide treatments in host plants etc. (Abd Allah et al., 2015). Few microbial communities are found to be present all over the plant and are known as plant-associated genera. The degree of specificity is based on the colonization of microbes and habitats (Chen et al., 2016). Such associations are passed on to next generation through seeds (Hardoim et al., 2012), pollen grains. Moses is considered as oldest living plant and they transfer from sporophyte to the gametophyte and vice versa (Bragina et al., 2012).

Medicinal plants harbor a distinctive microbiome due to their unique and structurally divergent bioactive secondary metabolites that are most likely responsible for the high specificity of the associated microorganisms (Khan et al., 2017).Distribution of these microbes depends on age, environmental factors and genetic background . Endophytes present in active tissues of plants are important part of ecosystem. Some of them have established an interaction that influence the production of natural compounds thereby affecting the amount of plant derived drugs .

Interaction of host medicinal plants with endophytic organisms

Endophytic microorganisms have a symbiotic relationship with the host medicinal plants.They provide specific advantages to plants such as nitrogen fixation. They also produce biologically active secondary metabolites such as alkaloids, flavonoids, terpenes/terpenoids, polyphenols, xanthenes, anthraquinones, cytochalasins, benzofurans, steroids, lignans, polysaccharides and plant growth hormones. Many of these compounds have therapeutic applications such as antimicrobial, antioxidant, anticancer, and anti-inflammatory. Endophytic microbes also constitute an important source for drug discovery. Plants and their parts have been used as a source of medicinal bioactive compounds against numerous forms of ailments since time immemorial. The traditional medicinal systems of Asia, such as Ayurveda, Siddha, Tibetan and Chinese systems have found and used the therapeutic value of numerous plants for curing diseases and healing injuries using natural medicines widely distributed throughout the globe.

Many plants harbor microbial endophytes within their tissues without any symptoms of infection; the symptomless interaction with microbes is apparently non pathogenic to weakly or slightly pathogenic depending upon the type of microbial species. The presence of endophytes in plant tissues has profound influence on the inclusive fitness, their interactions with pathogens, and the production of bioactive compounds of pharmaceutical importance (Maheshwari 2017; Rosenblueth and Martı´nezRomero 2006).

The most common examples of the association of a microbe with a plant can be that of nitrogen-fixing bacteria in leguminous plants, or the close association of fungi and plant in the form of mycorrhizae. The infections caused to plant tissues are symptomless their isolation and identification is done by dissecting the plant tissue via laboratory analysis (Franche et al. 2009; Burns and Hardy 2012).

Medicinal plants are traditionally used worldwide as remedies for the treatment of various diseases and the composition of bioactive compounds produced by these medicinal plants varies widely depending on the plant species and their association with microbes. Although, a vast majority of medicinal plants have been well-studied with respect to their phytochemical constituents and respective pharmacological properties, interactions between host and microbes remain poorly understood (Ko¨berl et al. 2013).

Recently, research on endophytic microorganisms has increased due to their intimate interaction with the host species, and it is believed that the phytochemical constituents of plants are related directly or indirectly to the interactions of endophytic organisms with their host. Asia is a continent which harbors numerous medicinal plants with potent biological activities. In fact, many of the biological and therapeutic activities of these plants are due the association with fungal or bacterial endophytes.

The colonization by endophytes of host plants is influenced by specific chemicals produced by host plants that induce chemotaxis (Badri et al. 2009). Through long-term coevolution of endophytes different types of secondary metabolites are produced by the host plants as a resistance mechanism to pathogens. Hence, the host secondary metabolites, which act as obstacles for the colonization of endophytes, induce the secretion of matching detoxification enzymes such as cellulase, lactase, xylanase, and protease, by the endophytes (Jia et al. 2016).

During the long period of co-existence and evolutionary co-adaptation, endophytes can establish different types of relationships/interactions with the host plants, which may be categorized as a continuum of mutualism, antagonism, or neutralism. The factors affecting on the population structure of the endophytes are the genetic background, nutrient level, and ecological habitats of the host plants. These factors, in turn, confer some benefits, such as the induced growth, increased resistance to diseases, and accumulation of bioactive compounds (Fira´kova´ et al. 2007). Hence, the mutual interaction between endophytes and host plants can influence the formation of certain bioactive compounds having medicinal properties, which can be used by humans. In other words, the presence of endophytes can enhance the medicinal properties of the host plants

Growth of host plants

Endophytic bacteria are the plant beneficial bacteria that thrive inside plants and can improve plant growth under normal and challenging conditions. They can benefit host plants directly by improving plant nutrient uptake and by modulating growth and stress related phytohormones. Indirectly, endophytic bacteria can improve plant health by targeting pests and pathogens with antibiotics, hydrolytic enzymes, nutrient limitation, and by priming plant defenses. To confer these benefits, the bacteria have to colonize the plant endosphere after colonizing the rhizosphere. The colonization is achieved using a battery of traits involving motility, attachment, plant-polymer degradation, and evasion of plant defenses .

Endophytic bacteria have been shown to impart several beneficial effects on their plant host directly or indirectly. They can benefit plants directly by assisting plants in getting nutrients, and improve plant growth by modulating growth related hormones, which can help plants grow better under normal and stressed conditions (Ma et al., 2016). Indirectly, endophytic bacteria improve plant growth by discouraging phytopathogens using mechanisms like antibiotic and lytic enzyme production, nutrient unavailability for the pathogens, and priming plant defense mechanisms and thereby protecting the plants from future attacks by pathogens (Miliute et al., 2015).

Endophytic bacteria enhance the host plant growth indirectly by discouraging the growth of phytopathogens and plant pests. They can produce substances that can antagonize phytopathogens, like antibiotics, toxins, siderophores, hydrolytic enzymes and antimicrobial volatile organic compounds (Sheoran et al., 2015). Both bacterial and fungal pathogens can be targeted by endophytic bacteria (Lodewyckx et al., 2002). Bacteria belonging to *Actinobacteria*, Bacillus, Enterobacteor, Paenibacillus, Pseudomonas and *Serratia* are the most commonly reported genera for their antimicrobial activity against phytopathogens (Aktuganov et al., 2008; Liu et al., 2010). Endophytic bacteria have been demonstrated to successfully suppress fungal disease in plants like black pepper, potato and wheat (Aravind et al., 2009).

Availability of Nutrients to host plants

Soils usually lack a sufficient quantity of one or more of the nutrient compounds necessary for plant growth. The endophytic bacteria can help their host plants in getting increased amounts of limiting plant nutrients, which include nitrogen, iron, and phosphorus (Glick, 2012). Endophytic bacteria can increase the nitrogen availability for their host plants. These bacteria can supply fixed atmospheric nitrogen to their host plants by expressing nitrogenase activity (Montanez et al., 2012). Nitrogenase is a highly conserved protein and all N_2 fixing bacteria have this enzyme, with ample evidence suggesting lateral gene transfer (Ivleva et al., 2016).

Nitrogen fixing bacteria like *Azoarcus* sp.BH72, *Gluconacetbacter diazotrophicus*, *Azospirillum brasilense*, *Burkholderia* spp. and *Herbaspirillum seropedicae* have been reported to increase the host plant biomass by N_2 fixation under controlled conditions (Bhattacharjee et al., 2008). Associative nitrogen-fixing endophytes perform better than rhizosphere microorganisms in enabling plants to thrive in nitrogen limited soil environments and promote plant health and growth. Gupta et al. (2013) reported that endophytic nitrogen-fixing bacteria may also enhance the rate of nitrogen fixation and accumulation in plants residing in nitrogen limited soils. Endophytic bacteria are not as efficient as rootnodule associated *Rhizobium* in Nitrogen-fixation ability.

Endophytic bacteria can increase the availability of phosphorus for the plants by solubilizing precipitated phosphates, using mechanisms like acidification, chelation, ion exchange and production of organic acids (Nautiyal et al., 2000). They can also increase phosphorus availability in the soil by secreting acid phosphatase that can mineralize organic phosphorus (Van Der Heijden et al., 2008). Moreover, endophytic bacteria can prevent phosphate adsorption and fixation under phosphate-limiting conditions by assimilating solubilized phosphorus. Thus, these bacteria can act as a sink to provide phosphorus to the plants when they need it.

Stress resistance in host plants

The symbiotic interactions between plant and endophyte may result in several outcomes as defined by fitness benefits by each of the partners (Lewis, 1985). Benefits to host plants can be positive (mutualism), neutral (commensalism and neutralism) or negative (parasitism, competition and amensalism). Variations in the outside environment put the plant metabolism out of homeostasis, which creates necessity for the plant to harbour some advanced genetic and metabolic mechanisms within its cellular system (Kaul et al., 2016). Herein, the importance of microbes, especially the endophytes, increases immensely. Endophytic microbes aid in plant health by deterring herbivory and pathogenesis while also facilitating plant growth through nutrient uptake (modification of root morphology, alteration of nitrogen accumulation and metabolism), water use efficiency (osmotic adjustment, stomatal regulation) and curtailing of environmental stresses. The endophytes, in return, obtain access to the host plant's nutrients and dissemination to the next generation.

Symbiotically conferred abiotic stress tolerance involves at least two mechanisms: (i) activation of host stress response systems soon after exposure to stress, allowing the plants to avoid or mitigate the impacts of the stress (Redman et al. 1999) and (ii) biosynthesis of antistress biochemicals by endophytes . Studies conducted on *Arthrobacter* sp. and *Bacillus* sp. isolated from pepper plant showed significant reduction in upregulation and even downregulation of some stress-inducible genes. *Phoma glomerata* and *Penicillium* sp. significantly increased plant biomass, related growth parameters, assimilation of essential nutrients, such as potassium, calcium, magnesium, and reduced the sodium toxicity in cucumber plants under sodium chloride and polyethylene glycol-induced salinity and drought stress when compared with control plants (Wiewiora et al. 2015).

Increase in Bioactive compounds in host plants

Plants as well as microorganisms associated with plants have come out with products with high therapeutic potential. Bioactive compounds are in high demand in the pharmaceuticals and naturopathy, due to their health benefits to human and plants. Microorganisms synthesize these compounds and some enzymes either alone or in association with plants. Microbes residing inside the plant tissues, known as endophytes, also produce an array of these compounds. Endophytic actinomycetes act as a promising resource of biotechnologically valuable bioactive compounds and secondary metabolites. Endophytic *Streptomyces* sp. produced some novel antibiotics which are effective against multi-drug-resistant bacteria Antimicrobial agents produced by endophytes are eco-friendly, toxic to pathogens and do not harm the human. Endophytic inoculation of the plants modulates the synthesis of bioactive compounds with high pharmaceutical properties besides promoting growth of the plants. Hydrolases, the extracellular enzymes, produced by endophytic bacteria, help the plants to establish systemic resistance against pathogens invasion. Phytohormones produced by endophytes play an essential role in plant development and drought resistance management (Singh et al., 2017).

Endophytes are reported to produce a number of bioactive metabolites in a single plant or microbe which served as an excellent source of drugs for treatment against various diseases and with potential applications in agriculture, medicine, food and cosmetics industries (Shukla et al., 2014). These secondary metabolites were categorized into various functional groups, alkaloids, benzopyranones, chinones, flavonoids, phenolic acids, quinones, steroids, saponins, tannins, terpenoids, tetralones, xanthones, and many others (Ahsan et al., 2017; Godstime et al., 2014). Extraction of metabolites from endophytes is affected by various factors, such as the season of sample collection, climatic condition and geographical location (Shukla et al., 2014). However, with a revolutionary synthetic process that has been developed during the past few years, extraction from plants and other natural sources has now become more feasible, efficient and convenient (Atanasov et al., 2015). The production of bioactive substances by endophytes, has been directly associated with the evolution of the host microorganisms, which may have incorporated genetic information from higher plants, allowing them to better adapt to the host plant and perform some functions, such as protection from various types of pathogens, insects, and grazing animals (Bogner et al., 2017). Some of the commonly found secondary bioactive compounds from endophytes are described below. Taxol (paclitaxol), a complex diterpene alkaloid produced by the endophyte *Metarhizium anisopliae* found in the bark of *Taxus* tree, is one of the most promising anticancer agents developed or synthesized to date (Visalakchi and Muthumary, 2010; Jalgaonwala et al., 2011). Camptothecin, from *Nothapodytes foetida* is known to have cytotoxic and antifungal properties (Carvalho et al., 2016).

Therapeutic applications of bioactive compounds from endophytic microorganisms

Endophytes act as reservoirs of novel bioactive secondary metabolites, such as alkaloids, phenolic acids, quinones, steroids, saponins, tannins, and terpenoids that serve as a potential candidate for antimicrobial, anti-insect, anticancer and many more properties. They can be readily isolated from any microbial or plant growth medium. While plant sources are being extensively explored for new chemical entities for therapeutic purposes, endophytic microbes also constitute an important source for drug discovery (Gouda et al., 2016).

Antibiotic Production

Infectious and parasitic diseases account for approximately half of the deaths worldwide (Menpara and Chanda, 2013). Although it is the generation of nano to pico drugs, natural sources have been proven as the best source for drug discovery. Medicinal plants and their endophytes are an important source of precious bioactive compounds and secondary metabolites that contribute to more than 80% of the natural drugs available in the market (Singh and Dubey, 2015). Endophytic microorganisms are the storehouse of novel secondary metabolites that can serve as an excellent source of drugs for antiarthritic, antimicrobial, anticancer, antidiabetic, anti-insect, and immunosuppressant activities (Godstime et al., 2014).

Antibiotics or hydrolytic enzymes can be released by endophytes present in plants to prevent colonization of microbial plant pathogens or to prevent insect and nematode infection. Endophytes can produce a variety of secondary metabolites also produced by their hosts. For example, anticancer drug camptothecin is a potential bioactive compound coproduced by the plants as well as their associated endophytes (Soujanya et al. 2017).

There are a number of bioactive compounds, such as camptothecin, diosgenin, hypericin, paclitaxel, podophyllotoxin, and vinblastine, which have been commercially produced by different endophytic fungi present in respective plants and they are of both agricultural as well pharmaceutical importance (Joseph and Priya, 2011; Zhao et al., 2011a). These compounds are analogs of various types of phytohormones, essential oils etc. isolated from various endophytes (Zhao et al., 2011b; Nicoletti and Fiorentino, 2015).

Anticancer compounds

Endophytes of medicinal plants are a great source of anticancer compounds with pharmaceutical value, such as Jammosporin A, Podophyllotoxin and Taxol. Taxol is a notable diterpenoid, originally isolated from the Pacific yew tree Taxus brevifolia. It has shown a promising activity against breast cancer. (Caruso et al. 2000).

Similarly, another compound, Versicoumarin A, with cytotoxic activity against human tumor cells, was obtained from *Aspergillus versicolor* isolated from *Paris marmorata* used in traditional Chinese medicine (Yan et al. 2016).

Monarda citriodora from the Indian state of Jammu and Kashmir have been shown to harbor 28 different fungal endophytes with anticancer and antimicrobial activities (Katoch et al. 2017).Terrein, a compound with antimicrobial and anti-tumor activity was obtained from an endophytic *Aspergillus terreus* isolated from the Indian medicinal plant *Achyranthes aspera* (Goutam et al. 2017).Brefeldin A, a lactone antiviral was isolated from an endophytic *Penicillium* sp. isolated from Panax notoginseng native to China. Its anticancer and antiviral activities have been reported (Xie et al. 2017).

Two novel cytochalasans, namely Phomopchalasins A and B with anticancer and anti-inflammatory potential have been isolated from an endophytic *Phomopsis* sp. fungus from Isodon eriocalyx, native to China .

Other therapeutic uses

The fungus *Colletotrichum gloeosporioides*, isolated from the medicinal plant *Huperzia serrata* native to China, is responsible for an effective treatment of Alzheimer's disease due to the production of Huperzine A (Caruso et al. 2000). Isolation of Allopurinol, a well known medication initially sold under the brand name Zyloprim, with activity against hyperuricemia, has been reported from a *Colletotrichum* sp. endophyte isolated from *Tinospora cordifolia*. Other endophytes from Asian medicinal plants have been reported to produce functional anti-inflammatory compounds, such as Asiaticoside and Ergoflavin.

Conclusion

Endophytes such as bacteria and fungi are associated with plants or have been colonized inside the plant tissues. Environmental factors like soil type and moisture, plant genotypes, age of plant etc. determine of the microbiota of plants. There are a number of microbiome studies undertaken for better understanding of associations and diversity of microbiota in plant system. The endophytic organisms in plants enhance their growth indirectly by protecting them from plant pathogens and pests. They also improve synthesis of substances like antibiotics, enzymes, toxins and other therapeutically important organic compounds .Different endophytes isolated from medicinal plants were found to produce effective bioactive compounds with notable therapeutic activities.The pressing need for novel chemical compounds targeting human diseases in order to curb drug-resistant microbes in life-threatening infections has recently stimulated research on novel bioactive compounds from endophytes present in medicinal plants.

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