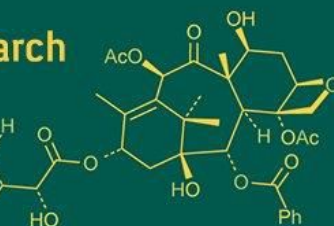
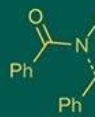


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Antimicrobial activity of endophytic bacteria present status and future perspectives

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Abstract

Antibiotic resistance is defined as the reduction of the effectiveness of an antibiotic during the treatment of infectious diseases. Gram-negative bacteria are more resistant than Gram-positive bacteria due to an outer lipopolysaccharide membrane in their cell wall, which limits antibiotic access to their targets in the bacterial cells. Other mechanisms contributing to antibiotic resistance in bacteria include modifying the antibiotic target site. (Aravamuthan *et al.*, 2010) ^[5] However, the discovery of new antimicrobial compounds from natural products has declined over the years and has reached a standstill compared to the Golden Antibiotic Age (1940-1960). Endophytic bacteria are ubiquitous in most plant species, either through their active colonisation of plant tissues or their latent residence. Endophytes are microorganisms that reside in the tissues of living plants. They are relatively unstudied and are potential sources of novel natural products for exploitation in medicine, agriculture, and industry. The endophytes of medicinal plants participate in biochemical pathways and produce novel bioactive compounds.

Keywords: Antimicrobial resistance, endophytic bacteria, antibacterial activity, bioactive metabolites

Introduction

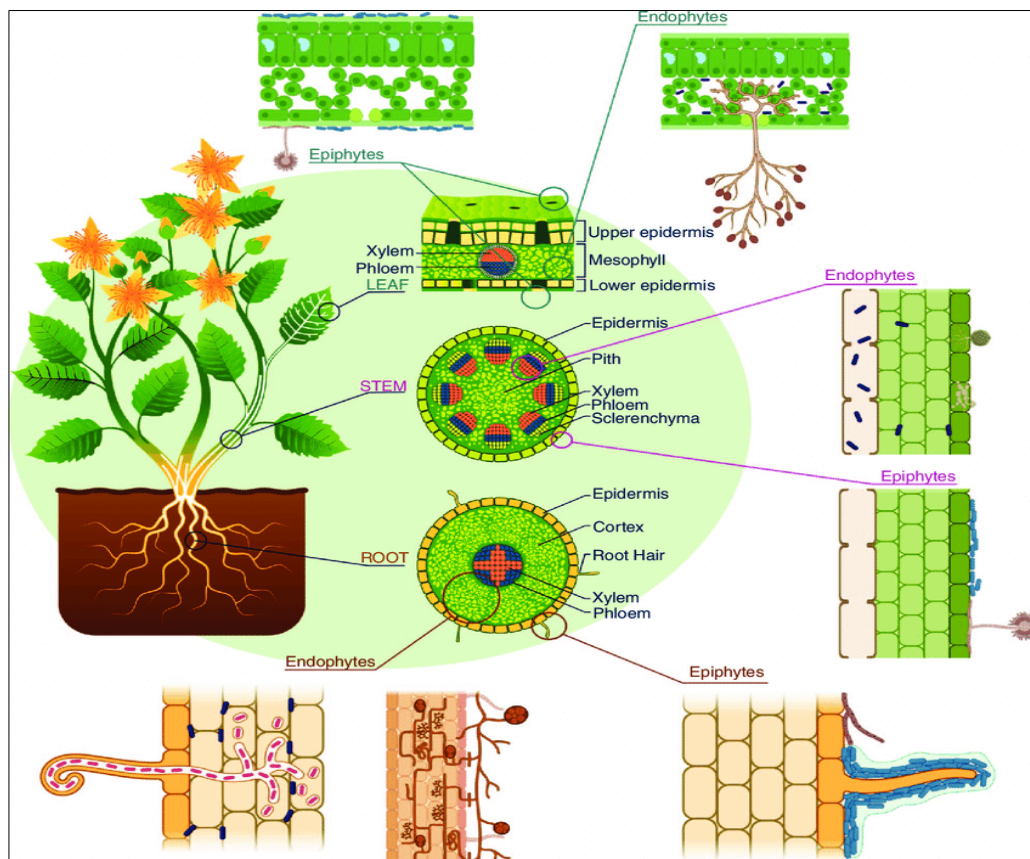
Antimicrobial resistance is one of the significant public health problems, especially in developing countries like India, where relatively easy availability and inappropriate use of antibiotics lead to a higher incidence of resistance. The world's human population is increasing alarmingly, and various new health issues are increasing. Research on antibiotics and other microbial natural products is pivotal in the global fight against the growing problem of antibiotic resistance. It is necessary to find new antibiotics to tackle this problem. Global health problems due to drug resistance among pathogenic microorganisms have necessitated the urgent need for new and effective antimicrobial agents. In recent years, the search for new therapeutic agents has been directed towards endophytes because these microbes produced several novel and interesting bioactive metabolites with multiple applications. Endophytes are ubiquitous organisms that live within the host plants without causing any apparent symptoms of disease (Sturz and Nowak, 2000) ^[52]. Endophytes are intracellular organisms often fungi and bacteria colonising plants' internal tissue, showing no external sign of infection or negative effect on their host. The relationship that they establish with the plant varies from symbiotic to pathogenic. Endophytes are an endosymbiotic group of microorganisms that colonise in plants and microbes that can be readily isolated from any microbial or plant growth medium. They 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. While plant sources are being extensively explored for new chemical entities for therapeutic purposes, endophytic microbes also constitute an important source for drug discovery. This review aims to comprehend the contribution and uses of endophytes as an impending source of drugs against various diseases and other possible medicinal uses.

Antimicrobial Resistance

Antimicrobial resistance (AMR) is a complex issue of global concern. The misuse of antibiotics in the medical, veterinary and agricultural sectors, which include the inappropriate prescribing of antibiotics, their overuse in the livestock sector and insufficient hygiene

practices in hospitals, all contribute to the rise of AMR. Global trade and travel are also accelerating the spread. At the same time, the development pipeline of new antibiotics has slowed, mainly due to insufficient incentives, allowing microorganisms to outpace the development of new drugs. The discovery of antibiotics meant previously lethal infections could be cured and surgical procedures made safer, allowing for the development of modern medicine. Micro-organisms are termed 'antimicrobial-resistant' or

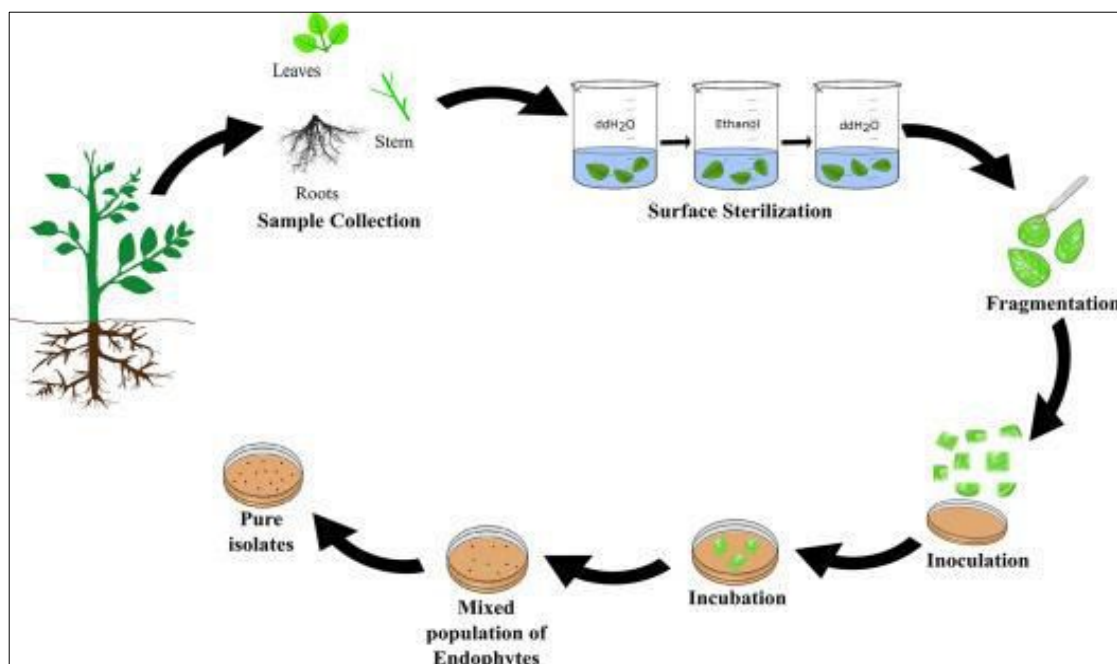
'drug-resistant' when they are no longer inhibited by an antimicrobial to which they were previously sensitive. Such resistance is called 'acquired resistance' and is encoded by resistance genes in the DNA of the microbe. Resistance genes can arise through spontaneous mutations in the microbial DNA, but some have evolved over many years due to natural selection by natural antimicrobials in the environment. (Merrett, 2013) [38].



Endophytic Bacteria

Endophytes are intracellular organism often fungi and bacteria colonize the internal tissue of plants showing no

external sign of infection or negative effect on their host. The relationship that they establish with the plant varies from symbiotic to pathogenic (Sturz and Nowak, 2000) [52].



Bioprospecting of Endophytes

Types of Endophytes

Endophytes are associated with plants in various forms, including bacteria (actinomycetes or mycoplasma) or fungi that have been colonized inside the plant tissues. More than 200 genera from 16 phyla of bacterial species have been reported to be associated with endophytes and among them, most of the species belong to the phyla Actinobacteria, Proteobacteria, and Firmicutes (Golinska *et al.*, 2015) [23].

The diversity of endophytic bacteria ranges from gram-positive to gram-negative bacteria, such as *Achromobacter*, *Acinetobacter*, *Agrobacterium*, *Bacillus*, *Brevibacterium*, *Microbacterium*, *Pseudomonas*, *Xanthomonas* etc. (Sun *et al.*, 2013) [54]. Bacterial endophytes are diverse in nature and are known to produce different bioactive metabolites that act as antimicrobial and anticancer compounds, for example, with 76% of them reported from the single genus, *Streptomyces*.

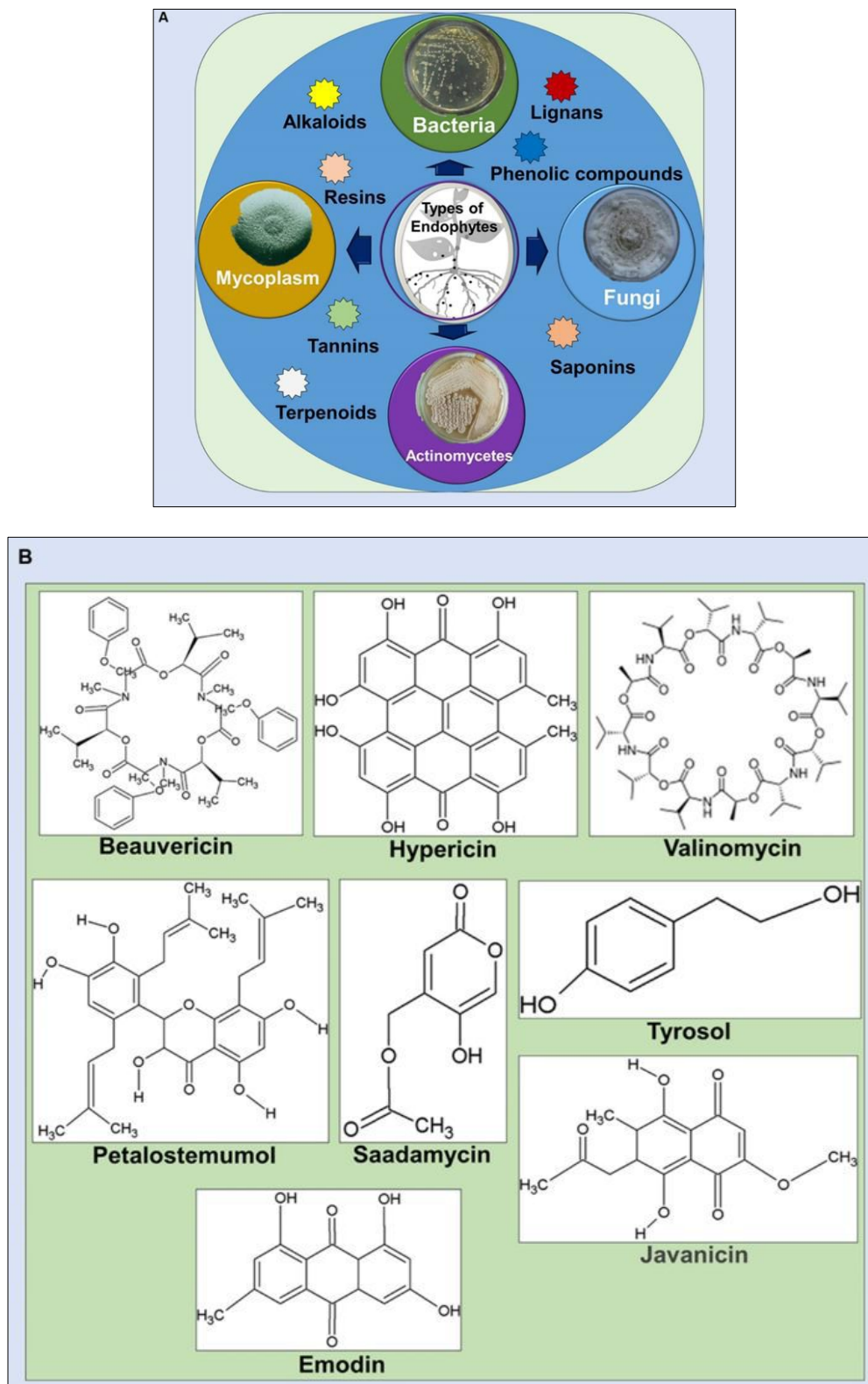


Fig 1: A: Types of endophytes and the bioactive compound groups associated with them B: Selected bioactive compounds with medicinal importance isolated from endophytes

Distribution and diversity of endophytes

Almost all vascular plant species examined to date were found to harbour endophytic bacteria or fungi. Surveys of various hosts during the past 20 years have demonstrated that the colonization of land plants by endophytes is ubiquitous. Endophytes are detected in plants growing in tropical, temperate and boreal forests, with the hosts ranging from herbaceous plants in various habitats, including extreme arctic, alpine and xeric environments to mesic, temperate and tropical forests. Moreover, the colonization of endophytes in marine algae, mosses, ferns, fern allies, numerous angiosperms, and gymnosperms, including tropical palms, broad-leaved trees, estuarine plants, diverse herbaceous annuals, many deciduous and evergreen perennials has also been recorded.

Endophytes are found in a wide variety of plant tissue types such as seeds, ovules, fruits, stems, roots, leaves, tubers, buds, xylem, rachis and bark. A perusal of the literature over the past decades indicated many ethnomedicinal plant species with rich botanical history, sampled from unique ecological niches and species, are known to harbour potential endophytic microbes (Strobel and Daisy, 2003) [51]. There are approximately 3,00,000 different plant species on our planet. An estimate of 1 million endophytes seems reasonable if each individual higher plant hosts an average of one to few endophytic strains. As a matter of fact, endophytes are important components of microbial biodiversity. Commonly, several to hundreds of endophytic species can be isolated from a single plant and among them, at least one species shows host specificity. The environmental conditions under which the host is growing also affect the endophyte population, and the endophyte profile may be more diversified in the tropical area. Endophytes are presumably ubiquitous in the plant kingdom with the population being dependent on host species and location. Many studies have tried to determine whether endophytes exhibit tissue specificity or host-specificity, but the results are contradictory with indications of both host-specificity and host generalism.

Anti-microbial effect of endophytes:

Bioactive metabolites are those low molecular weight organic molecules which are produced by microorganisms that are active at low concentrations against other microorganisms (Guo *et al.* 2008) [24]. Endophytic microbes

produced secondary metabolites active against pathogenic microbes (Tan and Zou, 2001) [56]. In the previous studies, it was reported that a large number of bioactive compounds isolated from endophytes, belonging to different classes like peptides, steroids, terpenoids, phenols, alkaloids, quinines and flavones (Yu *et al.*, 2010) [60]. Extraction of novel antibiotic metabolites from endophytes is an alternative to reduce the increasing level of drug resistance in pathogens. To date, a fewer effective antibiotic has been discovered against a wide range of pathogens, and less target specificity probably leads to an unfavourable return on investment (Yu *et al.*, 2010; Song, 2008) [60, 50]. The antimicrobial compounds are not only used 1663 International Journal of Chemical Studies as drugs for humankind but can also use to control foodborne diseases and food spoilage, a serious issue no endophytic microbe present on different host shows antifungal activities e.g. *Xylaria* sp. Many bioactive compounds are isolated from different hosts, such as sordaricin shows antifungal activity against *Candida albicans*. Similarly, bioactive metabolite million, 1, 8-dihydroxynaphthol 1-o-a-glucopyranoside had activity against the herpes simplex virus (Pittayakhajonwut *et al.*, 2005) [40].

Bioactive secondary metabolites of endophytic bacteria

Literature shows that some bacteria which live attached to plants have the ability to promote plant growth. (Compant *et al.*, 2010; Beneduzi *et al.*, 2013) [13, 8]. Endophytes provide a wide variety of bioactive secondary metabolites with unique structures, including alkaloids, benzopyran, chinones, flavonoids, phenolic acids, terpenoids etc.

Increased bioactive compound accumulation in medicinal plants

Research on endophytic bacterial contribution to their medicinal host plant metabolism is complicated by the fact that some secondary metabolites may be produced by the combined activity of both the bacteria and the host (Brader *et al.*, 2014) [11]. Some endophytic bacteria are known to induce the production of secondary metabolites in medicinal plants (Tiwari *et al.*, 2010) [57]. For example, *Bacillus altitudinis* serves as an effective elicitor that increases ginsenoside concentrations in the valuable medicinal herb, ginseng.

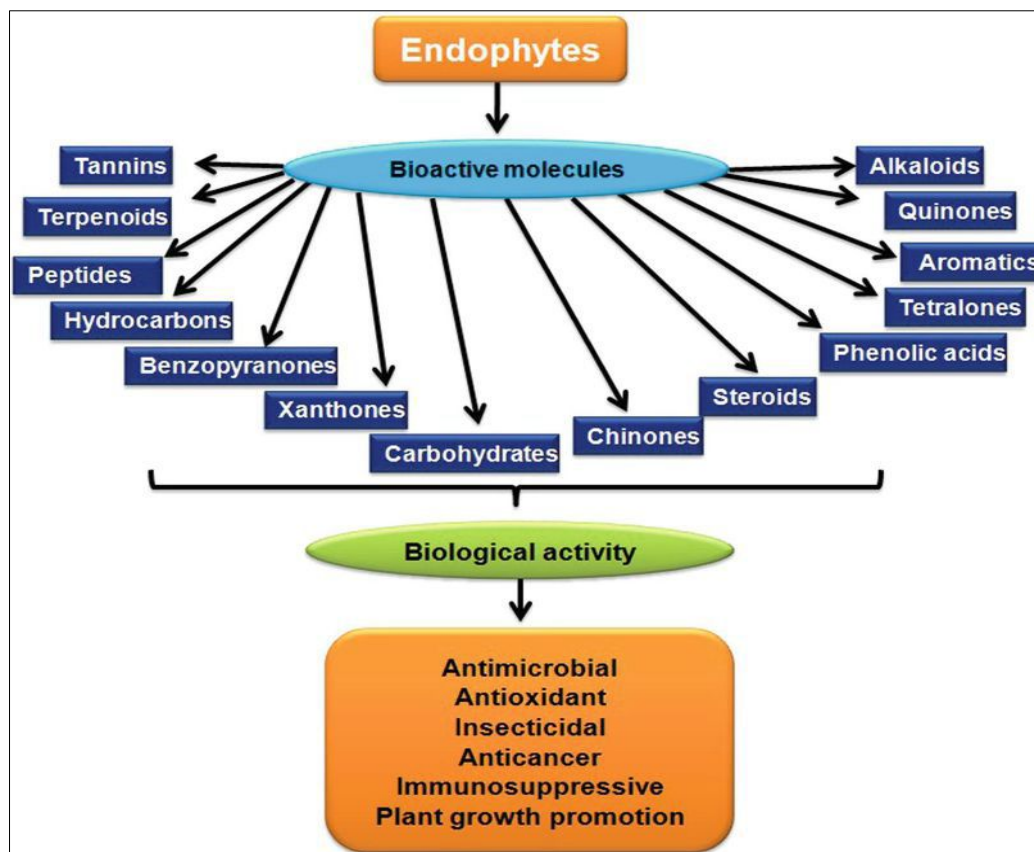
Medicinal uses of secondary metabolites of endophytic bacteria

Class	Compound	Endophytic bacteria	Host plant	Bio properties	References
Alkaloids	6-Prenylindole1-Acetyl-β-carboline Aeromicrobium Ponti Vochysia divergens Camptothecin	<i>Streptomyces</i> sp. <i>Aeromicrobium</i> point <i>Kytococcus</i>	<i>Allium tuberosum</i> <i>Vochysia divergens</i> <i>Ephedra foliata</i>	Antifungal activity Antibacterial activity Anticancer activity	Dubey, 2018 [48] Ghiasvand <i>et al.</i> , 2019 [22]
Alkaloid	2,3-dihydro-2,2-dimethyl-4(1H)-quinazolinone	<i>Streptomyces</i> sp.	<i>Lychnophora ericoides</i>	Anticancer activity	Conti <i>et al.</i> , 2016 [14]
Sesquiterpenes	Trichodones A-C Guignardieremophila	<i>Xiamycin</i> <i>Streptomyces</i> sp.	<i>Bruguiera gymnorrhiza</i>	Anti-HIV activity Anti-inflammatory activity	Ding <i>et al.</i> , 2010 [18] Liu <i>et al.</i> , 2015 [36]
Polyketones Lactones	A-E Guignardia mangiferae Gelsemium Polyketones Grignard dene A Guignardia mangiferae Naphthomycins A, D, E, L, K, O-Q	<i>Streptomyces</i> sp.	<i>Gelsemium elegans</i>	Antimicrobial activity Antifungal, antibacterial activities	Sasaki <i>et al.</i> , 2001 [46]

Natural products from endophytic bacteria

Many endophytes are members of common soil bacterial genera, such as *Pseudomonas*, *Burkholder* and *Bacillus* (Lodewyckx *et al.*, 2002) [37]. These genera are well known for their diverse range of secondary metabolic products including antibiotics, anticancer compounds, volatile organic compounds, antifungal, antiviral, insecticidal and immunosuppressant agents. While a wide range of

biologically active compounds have been isolated from endophytic organisms, they still remain a relatively untapped source of novel natural products. While most research has focused on fungal-based production of antimicrobial products, a number of low-molecular-weight compounds, active at low concentrations against a range of human, animal and plant pathogenic bacteria, have been isolated from bacterial endophytes.



Natural products from endophytic bacteria

Functions of endophytes:

Some endophytes have no apparent effects on plant development and growth, live on compounds produced by plants, they are known as commensal endophytes. Some endophyte has a beneficial impact on host plants, such as the production of plant growth hormones, protection against biotic stress by targeting invading pathogens, production of antibiotics against invading pathogens and induced systematic resistance inside the host plants (Hardoim *et al.*, 2015) [9]. A third group of endophytes showed detrimental effects on plants. Generally, endophytes have a neutral impact on plants during normal growth conditions, while they are more beneficial and showed a positive impact on plants during intensive conditions during the plant life cycle in short during intensive conditions, endophytes act like an army providing defence as well as need-based requirements to the host plant (Verma *et al.*, 2019) [59] e.g., fungus *Fusarium verticillioides* play both roles as a pathogen as well as beneficial endophytes in maize. The same endophyte acts differently on different plants; one plant acts symbiotic, while another acts in a detrimental manner. Even for the same plant, endophytes have different roles; in one phase of the life cycle become damaging, and in another, harsh environmental conditions become beneficial. The balance between the two states depends on the species type and environmental conditions (abiotic stress). The behaviour of endophytes inside plant hosts varies in different stages of

the life cycle. E.g., *verticillioides* repress the growth of additional pathogenic fungus, *Ustilagomaydis*, and protect their host from diseases. Clavicipitaceous fungi produced neurotoxic indol.

Endophytes play an important role in the defense system of plants. As the life cycle of endophytes is shorter than the life cycle of the host plant, they develop in very large numbers inside the host plant, resulting in a higher collection of antagonistic forms that are resistant to plant pathogens and herbivores. Communications and interactions among large endophytic populations are brought through signal exchange via growth factors and antibiotic molecules. Siderophore production by microbes causes the sequestration of iron (Fe) molecules necessary for the growth of plant pathogens. Therefore, this indirect mechanism of iron sequestration protects the plant from pathogenic fungi attack (Hardoim *et al.*, 2015) [9]. There is increasing evidence that at a suitable, interactions among valuable microbes and plants cause an immune response in plants similar to that of pathogens. Still, later on, mutualists run away host defence responses as well they are able to successfully colonise plants (Aly *et al.*, 2011) [3].

Present status of endophytic bacteria

The use of therapeutic plant species in traditional medicine is as old as mankind and currently, it is estimated that almost all of the world's plants (3,00,000) host one or more

endophytes (Strobel and Daisy, 2003)^[51]. India is among the most biodiverse region of the world and thousands of plant varieties are found in different parts of the country in their different agro-climatic zones. Many of these plants have yet to screen for the presence of endophytic bacteria and their potential antibacterial activity. The natural therapeutic compounds produced by endophytic bacteria have several potential applications in the pharmaceutical industry. The endophytic bacteria-derived natural products such as Ecomycins, Pseudomycin, Munumbicin, and Xiamycins have antibacterial, antimycotic and antiplasmodial activities. (Christina *et al.*, 2013)^[12].

Identification and isolation of endophytic bacteria

Study on identified and characterized endophytic bacteria from Avocado and Black grapes. All the bacterial isolates were Gram-positive and belong to the genus *Bacillus*. The isolates were tested for enzyme production assays and were found positive for catalase and lipase enzymes. Two isolates from black grapes were protease-positive (Prasad and Dagar, 2014)^[41].

Investigation of isolation, identification, and to assess the antibacterial activity of endophytic bacteria isolated from different varieties of babool leaves *viz.* *Acacia nilotica*, *Acacia catechu* and *Acacia auriculiformis*. 18 endophytic bacteria, each from three varieties of babool leaves, had been isolated and identified by sequencing of the 16S rRNA gene. The isolated endophytic bacteria were identified as *Staphylococcus aureus*, *Bacillus humi*, and *Lysinibacillus sarlettae*. Considerable antibacterial activities against a panel of human pathogenic microorganisms (*Staphylococcus aureus*, *Streptococcus pyogenes*, *Bacillus cereus*, *Klebsiella pneumonia*, and *Salmonella* 12 and *Escherichia coli*) were recorded. Out of 18 isolates of endophytic bacteria from *Acacia nilotica*, 12 were effective against *Staphylococcus aureus*. Among 18 isolates of endophytic bacteria from *Acacia catechu*, 15 isolates had shown inhibitory activity against *Klebsiella pneumonia*. No considerable antibacterial activity was observed from endophytic bacterial isolates from *Acacia auriculiformis* (Soman, 2018)^[49].

To study the isolation and identification of endophytic bacteria producing bright red pigment from the dye-yielding plant *Beta vulgaris* L. 17 endophytic bacteria were isolated, and out of that one bacterial isolate, KC1 secreted red pigment. The isolate KC1 was found to be a *Coccobacillus*, gram-negative, which gave a catalase-positive reaction, and after molecular identification, it was identified as *Serratia marcescens* strain VIT-PTS (Khanam and Chandra, 2015)^[31].

Documentation of endophytic bacteria

Of the endophytic strains, almost 853 were isolated from aerial tissues of four agronomic crop species and 27 prairie plant species. They determined several phenotypic properties and found approximately equal numbers of gram-negative and gram-positive isolates. In a greenhouse study, 28 of 86 prairie plant endophytes were found to colonize their original hosts at 42 days post-inoculation at levels of 3.5 to 7.7 log₁₀ CFU/g (fresh weight). This study first defines the endophytic nature of *Microbacterium testaceum* which may be useful for biocontrol and other applications (Shimels *et al.*, 2020)^[47].

The study was carried out on characterisation of the culturable endophytic bacteria of common bean (*Phaseolus vulgaris*) leaves from three different cultivars (*Vermelhinho*, *Talismã*, and *Ouro Negro*) grown under the same field conditions. (6) The density of endophytic populations varied from 4.5 x 10² to 2.8 x 10³ CFU g⁻¹ of fresh weight. Out of the 158 total isolates, 36.7 per cent belonged to the *Proteobacteria*, 32.9 per cent to *Firmicutes*, 29.7 per cent to *Actinobacteria* and 0.6 per cent to *Bacteroidetes*. The three *P. vulgaris* cultivars showed class distribution differences among *Actinobacteria*, *Alphaproteobacteria*, and *Bacilli*. Based on 16S rDNA sequences, 23 genera were isolated, comprising bacteria commonly associated with soil and plants. The genera *Bacillus*, *Delftia*, *Methylobacterium*, *Microbacterium*, *Paenibacillus*, *Staphylococcus* and *Stenotrophomonas* were isolated from all three cultivars (Denise *et al.*, 2002)^[17]. Investigation A total of one hundred and thirty-two endophytes were isolated from different healthy parts, such as leaves, stems, fruits and roots of the four ethnomedicinal plants under investigation. Secondary metabolites having application in the medicinal pharmaceutical areas were also studied. Some endophytic microorganisms can produce the same secondary metabolites as that of the plant, thus making them a promising source of novel compounds (Costa *et al.*, 2012)^[15].

Reports were also noted on endophytic bacteria isolated from the *Plectranthus tenuiflorus* medicinal plant in the Saudi Arabian Desert and studied their antimicrobial activities. Endophytic bacteria were isolated from the roots, stems and leaves of the *Plectranthus tenuiflorus* plant. Among 28 endophytic bacterial isolates from different organs of the *Paenibacillus tenuiflorus* plant, 8 isolates were identified by partial sequencing of their 16S rRNA gene. The isolated endophytic bacteria were *Bacillus sp.*, *Bacillus megaterium*, *Bacillus pumilus*, *Bacillus licheniformis*, *Micrococculuteus*, *Paenibacillus sp.*, *Pseudomonas sp.*, and *Acinetobacter calcoaceticus*. Most isolates that exhibited extracellular enzymatic activity belong to the genus *Bacillus*. Furthermore, *Bacillus sp.* (HE613660) exhibited stronger activities in extracellular enzymes such as *amylase*, *esterase*, *lipase*, *protease*, *pectinase*, *xylanase* and *cellulase* than other strains (El-Deeb *et al.*, 2013)^[19].

The study was carried out on isolated endophytic bacteria from different parts of plants, such as root, stem and leaves samples of mangrove plants and processed immediately after surface sterilisation by standard procedure. Isolation and purification of endophytic bacteria was done by using starch casein agar with antibiotics to inhibit the growth of fungi. *In vitro* screening was done to identify the antibacterial activity of endophytic bacteria by agar gel diffusion method against nine different clinical pathogens *viz.*, *Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, *Proteus mirabilis*, *Klebsiella* species, *Pseudomonas fluorescence*, *Pseudomonas aeruginous*, *Salmonella typhi* and *Streptococcus pyogenes*. A total of 24 isolates were recovered from all the samples. Out of 24 isolates, nine were from root, eight from stem and seven from leaf samples (Gayathri and Murlikrishnan, 2013)^[21].

A study was carried out for the occurrence, distribution, growth-promoting and antifungal activities of endophytes in the root of *Salvia miltiorrhiza*. Six endophytic bacterial strains, *Pseudomonas*, *Rhizobium*, *Bacillus* and *Novosphingobium*, were isolated from the root of healthy *S.*

multiorrhiza. Their work indicates that endophytic bacteria occur in the root of *S. multiorrhiza* and that associated bacterial isolates have a growth-promoting effect on muskmelon seeds and are expected to be a potential source of bioactive metabolites (Jia *et al.*, 2013) [29].

I assessed the isolated 576 endophytic bacteria from the leaves, stem, and roots of 10 rice cultivars and identified 12 as diazotrophic bacteria using a specific primer set of *nif* genes. Through 16S rDNA sequence analysis, *nif* genes were confirmed in the two species of *Paenibacillus*, three species of *Microbacterium*, three *Bacillus* species and four species of *Klebsiella*. Among the 12 isolates tested, 10 strains showed higher auxin-producing activity, 6 isolates were confirmed as strains with high siderophore-producing activity, and 4 isolates had high phosphate solubilising activity. The results suggested that the endophytic diazotrophic bacteria characterised in the study could be successfully used to promote plant growth (Ji *et al.*, 2014) [28].

A study assessed the ability of twenty-nine endophytic bacteria isolated from the tissues of ryegrass (*Lolium perenne* L.). Most isolates belong to the genus *Pseudomonas* and showed multiple plant growth-promoting abilities. All tested bacteria exhibited the ability to produce indole-3-acetic acid and were sensitive to streptomycin. These strains were capable of phosphate solubilisation (62%), cellulolytic enzyme production (62%), a capacity for motility (55%) as well as for the production of siderophore (45%), ammonium (41%) and hydrogen cyanide (38%). Only five endophytes had the emulsification ability that resulted from the production of biosurfactants. The 1-amino cyclopropane-1-carboxylate deaminase (ACCD) gene (*acdS*) was found in ten strains. These bacteria exhibited ACCD activities in the range from 1.8 to 56.6 I mol of α -ketobutyrate mg⁻¹ h⁻¹, which suggests that these strains may be able to modulate ethylene levels and enhance plant growth (Kukla *et al.*, 2014) [33].

Identification and Characterization of endophytic bacteria from Avocado and Black grapes was done. All the bacterial isolates were Gram-positive and belong to the genus *Bacillus*. The isolates were tested for enzyme production assays and were found positive for catalase and lipase enzymes. Two isolates from black grapes were protease-positive (Prasad and Dagar, 2014) [41].

Inspection of the endophytic bacterial diversity associated with white turmeric was done. The isolation of endophytic bacteria was carried out using four kinds of media (Nutrient Agar (NA), NA contained white turmeric extract (NAT), Water Yeast Extract Agar (WYEA), WYEA contained white turmeric extract (WYEAT) and two methods of spread plate and plant piece methods. A total of 207 bacterial colonies were isolated from rhizomes, stems and leaves and 73 endophytic bacteria were selected based on morphological characteristics. Based on 16S rDNA sequence analysis, the isolates were from the cluster *Alphaproteobacteria*, *Betaproteobacteria*, *Gamma proteobacteria*, *Firmicutes* and *Actinobacteria* (Tirratna *et al.*, 2014) [58].

Isolation of 35 endophytic bacteria from *Catharanthus roseus*, *Ocimum sanctum*, *Mentha arvensis* and *Stevia rebaudiana*. 18 isolates were found to be Gram-positive cocci, 11 were Gram-negative bacilli, and 6 were found to be Gram-positive bacilli (Anjum and Chandra, 2015) [4].

Conduction of a study on isolation and identification of endophytic bacteria producing bright red pigment from the dye-yielding plant *Beta vulgaris* L. 17 endophytic bacteria were isolated, and out of that one bacterial isolate, KC1 secreted red pigment. The isolate KC1 was found to be a *coccobacillus*, gram-negative, which gave a catalase-positive reaction, and after molecular identification, it was identified as *Serratia marcescens* strain VIT-PTS (Khanam and Chandra, 2015) [31].

The plant roots are potential hosts to many beneficial microorganisms, including mycorrhizal fungi, rhizobia bacteria, antagonistic yeasts and endophytic fungi. They further stated that endophytic bacteria live symbiotically with the plant, helping the plant in several ways. They isolate and identify bacterial endophytes from the root and leaf tissue of *Prosopis cineraria*. A total of two endophytic bacteria were isolated from different parts of the plant. Based on the morphological and biochemical characterisation of the endophytes and 16S rRNA sequencing technique, *Bacillus subtilis* and *Stenotrophomonas maltophilia* were identified. Both the isolates *Bacillus subtilis* & *Stenotrophomonas maltophilia* were present in root tissue while only one i.e., *Stenotrophomonas maltophilia* isolated from leaf tissue (Rekha *et al.*, 2015) [43].

Fourteen endophytic bacterial isolates from the rhizome of *Curcuma longa* and characterised these isolates based on morphology, biochemical characteristics and 16S rRNA gene sequence analysis. The isolates were identified to six strains: *Bacillus cereus* (ECL1), *Bacillus thuringiensis* (ECL2), and *Bacillus species* (ECL3), *Bacillus tvdcumilis* (ECL4), *Pseudomonas putida* (ECL5) and *Clavibacter michiganensis* (ECL6). The strains were primarily sensitive to the antibiotic chloramphenicol, followed by erythromycin, while resistant to polymyxin B. The endophytic strains effectively inhibit the growth of *Escherichia coli*, *Klebsiella pneumoniae* and some of the fungal strains like *Fusarium solani* and *Alternaria alternata* (Ritu *et al.*, 2016) [44].

Using various enzymatic media, isolating 46 different rhizome and endophytic bacteria from the mangroves' soil, roots and leaves. These bacterial strains could produce industrially important enzymes (cellulase, protease, lipase and amylase). The bacteria were screened further for antagonistic activity against fungal pathogens. Finally, these bacterial strains were identified based on the 16S rDNA sequence. Taxonomic and phylogenetic analysis revealed 95.9-100 per cent sequence identity to type strains of related species. The dominant phylum was Gamma proteobacteria (γ -Proteobacteria), which comprised 10 different genera - *Erwinia*, *Vibrio*, *Psychrobacter*, *Aidingimonas*, *Marinobacter*, *Chromohalobacter*, *Halomonas*, *Microbulbifer* and *Alteromonas*. Firmicutes were the second dominant phylum, which contained only the genus *Bacillus* (Bibi *et al.*, 2017) [10].

A study was conducted to isolate, identify and assess the antibacterial activity of endophytic bacteria isolated from different varieties of babool leaves, viz. *Acacia nilotica*, *Acacia catechu* and *Acacia auriculiformis*. 18 endophytic bacteria each from three varieties of babool leaves had been isolated and identified by sequencing of 16S rRNA gene. The isolated endophytic bacteria were identified as *Staphylococcus aureus*, *Bacillus humi* and *Lysinibacillus arlettae*. Considerable antibacterial activities against a panel

of human pathogenic microorganisms (*Staphylococcus aureus*, *Streptococcus pyogenes*, *Bacillus cereus*, *Klebsiella pneumoniae*, and *Salmonella* 12 and *Escherichia coli*) were recorded. Out of 18 isolates of endophytic bacteria from *Acacia nilotica*, 12 were effective against *Staphylococcus aureus*. Among 18 isolates of endophytic bacteria from *Acacia catechu*, 15 isolates had shown inhibitory activity against *Klebsiella pneumoniae*. No considerable antibacterial activity was observed from endophytic bacterial isolates from *Acacia auriculiformis* (Soman, 2018) [49].

Antibacterial commotion of endophytic bacteria

Research was conducted to determine the presence of antibacterial activity in the extract of endophytes isolated from the medicinal plant *Andrographis paniculate* by agar gel diffusion method. In the study, leaves were used to isolate endophytic bacteria, and extracts were collected and screened against six human pathogenic bacteria and two pathogenic fish bacteria. The endophytic extract had activity against Gram-positive and Gram-negative bacterial pathogens (Arunachalam and Gayathri, 2010) [6].

The antimicrobial compound of endophytic bacteria obtained from Vinca roses, one of the most isolated endophytes, produced potential antimicrobial activity against some selected human pathogenic bacteria like *Bacillus cereus*, *Klebsiella pneumoniae*, *Vibrio cholera*, *Escherichia coli* and yeast *Candida albicans*. Morphological and biochemical characterisations indicated that the isolated strain Vrb 46 was similar to *Bacillus coagulans*. Thin-layer chromatography analysis of concentrated culture filtrate revealed several active UV bands on silica gel plates. Fermented cell-free broth was extracted with chloroform-methanol, and antimicrobial activity was found in the organic fraction (Roy and Banerjee, 2010) [45].

Use of *Pediococcus acid lactici* as a bacterial probiotic and 16000 broiler chickens were assigned in two experimental groups treatment (109 cfu/kg of feed of *Pediococcus acid* MA18/5M) and control. The administration of *Pediococcus acid lactic* positively affects the growth performance of broiler (2586.43vs2252.79 g, $p < 0.01$ and feed conversion ratio (2.00vs2.5) (Alloui *et al.*, 2012) [2].

The investigation was done on the antimicrobial activity of endophytic bacteria which were isolated from the medicinal plant *Memecylonedule* Roxb, *Tinospora cordifolia* Miers, *Phyllodium pulchellum* (Benth) Desv and *Dipterocarpus tuberculatus* Roxb in Thailand by agar well methods against four bacteria viz. *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and fungal pathogen, *Candida albicans*. These bacterial strains were investigated for the efficiency of solvents for extracting antimicrobial agents. The extract of UD25 isolate obtained from diethyl ether and chloroform was influential in inhibiting *Staphylococcus aureus*; it had bacteriostatic activity. The crude extract of diethyl ether and ethyl acetate could inhibit the growth of *Escherichia coli* and *Bacillus cereus*, giving them bactericidal activity. The suitable solvent for the other four isolates was ethyl acetate. The minimum inhibitory concentration (MIC) by microdilution broth test showed the lowest concentration of crude extract that inhibited the growth of pathogenic microorganisms in the range of 0.156 - 2.5 mg/ml. The minimum bactericidal concentration (MBC) was in the range of 0.312- 5 mg/ml. The most effective strain, UD25, was examined for morphological and biochemical properties and 16S rDNA. It

was identified as *Bacillus amylolique faciens* (Bhoonobtong *et al.*, 2012) [9].

A study was conducted on antimicrobial activities of secondary metabolites produced by endophytic bacteria from selected indigenous Kenyan plants. In the presence study the bacterial endophytes were isolated from the roots of *Cleodendrum myricoides*, *Lannea flavus*, *Dichrostac hyscinerea*, *Gompho carpus fruticosus*, *Balanites aegyptica*, *Jasminium floribundum* and *Hibiscus fuscus*. 21 endophytic bacteria were isolated and examined for their antimicrobial activities using the cross-streak method (Kaaria *et al.*, 2012) [30].

Work was carried on four economically significant papaya varieties viz: Red lady, Solo, Coorg honey and Bangalore and had isolated and characterized 18 endophytes. The phylogenetic analysis based on 16S rRNA sequence revealed that the *Bacillus* species is the predominant bacterial endophytes across papaya varieties (Krishnan *et al.*, 2012) [32].

Isolation, characterisation and antimicrobial activity of endophytic bacteria from *Polygonum cuspidatum* was performed. The result of the study showed that the endophytic bacteria in *P. cuspidatum* belong to five orders namely *Actinomycetales*, *Bacillales*, *Rhizobiales*, *Pseudomonas dales* and *Enterobacteriales*. The endophytic bacteria isolated from *P. cuspidatum* showed inhibitory activity against pathogenic fungi and bacteria (Sun *et al.*, 2013) [54].

Antibacterial activity of endophytic bacteria isolated from *Brassica oleracea* and identified the endophytic bacteria as *Pseudomonas aeruginosa* by various biochemical tests and 16S rRNA analysis. Two aspects of the endophyte were studied, namely enzyme quantification and antimicrobial activity. The enzyme activity was 2 IU/ml, 1.5 IU/ml and 1.9 IU/ml respectively for amylase, protease and cellulase. The endophyte had shown significant antimicrobial activity against *Klebsiella pneumoniae* NCIM 2883 (20 mm), *Staphylococcus aureus* ATCC 25923 (25 mm), *Escherichia coli* ATCC 25922 (13 mm) and *Salmonella typhi* ATCC 6539 (12 mm) (Sunkar and Nachiyar, 2013) [55].

Evaluation was done of the antimicrobial activity of endophytic bacteria isolated from *Terminalia Arjuna*, *Cantharanthus roseus* and *Azadirachta indica* against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Enterococcus faecalis* and *Candida albicans*. Of the several bacterial and fungal isolates, the bacterial isolate NRL2 exhibited a high antimicrobial activity against *Staphylococcus aureus*. The extract of NRL2 isolates obtained from methanol and ethanol was effective. The bacterial crude extract was used against Methicillin resistant *Staphylococcus aureus* by cup agar method (Kumar *et al.*, 2015) [34].

Evaluation of the antibacterial properties of endophytic bacteria isolated from a fern species *Equisetum arvense* Linn. against foodborne pathogenic bacteria was done. In the study, endophytic bacteria were isolated and identified based on 16S rRNA sequencing. Out of 103 identified endophytic bacteria, three species *Streptomyces albolongus*, *Dermacoccus* species and *Mycobacterium* species showed significant antibacterial activity against *Staphylococcus aureus* with inhibition zones of 45.34 ± 0.15 , 43.28 ± 0.19 and 22.98 ± 0.18 mm respectively (Das *et al.*, 2016) [16].

Isolation and identification of endophytic bacteria from the rambutan (*Nephelium lappaceum* L.) cultivar Binjai with

16S rRNA was done. Sequencing results showed that the bacterium was derived from *Corynebacterium*, *Bacillus*, *Chryseobacterium*, *Staphylococcus* and *Curtobacterium*. These endophytic bacteria were suspected to have an antipathogenicity mechanism. Some endophytic bacteria from rambutan fruit is also thought to belong to a group of plant growth promoting bacteria which produce auxin and gibberellins growth hormone (Suhandono *et al.*, 2016) [53].

Study was conducted on antimicrobial activity of endophytic bacterial populations isolated from medicinal plants of Iran. A total of 23 medicinal plant samples were collected, sterilised and crushed. Small pieces of the powdered samples were then cultured directly on three selective media. Grown colonies were identified by the 16S rRNA gene sequencing method. Each isolate was cultured in TSB (Tryptic Soy Broth) medium and then antimicrobial compound was extracted using ethyl acetate. Sixteen out of 23 bacterial isolates (69%) exhibited antimicrobial activity against the selected pathogenic bacteria such as *Bacillus cereus*, *Staphylococcus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Proteus mirabilis*, *Shigella Flexneri* and *Escherichia coli* (Beiranvand *et al.*, 2017) [17].

Evaluation of antimicrobial potential of endophytic bacteria isolated from leaf tissues of *Hyptissu aveolens* against some clinically significant pathogens. The results indicated that 60 percent of the isolates showed antimicrobial activity by inhibiting at least one of the test pathogens in preliminary screening. The isolates were identified as *Bacillus* and *Pseudomonas* species by morphological and biochemical characterisation. Phylogenetic analysis of 16S rDNA sequences of the isolates showed closest homology to *Bacillus amyloli quefaciens* and *Pseudomonas* sp. suggesting their endophytic nature. The crude ethyl acetate extracts prepared from fermentative broths exhibited moderate antibacterial and anticandidal activity by BLIS and agar diffusion assay. Enhanced antimicrobial activity was observed in the nutrient broth medium (Ipsita *et al.*, 2017) [26].

An assessment of the role of endophytic microbes in the therapeutic potential of *Fagonia indica* was done. 16S rRNA gene sequencing was used to identify isolated endophytic bacteria and also screened for antibacterial and antifungal activities by disc diffusion method. Their Minimum Inhibitory Concentration (MIC) were calculated by broth dilution method using microplate reader. Bacterial strains belonging to various genera (*Bacillus*, *Enterobacter*, *Pantoea*, *Erwinia* and *Stenotrophomonas*) were isolated and identified. Although all the extracts tested were active in inhibiting growth of selected pathogenic microbes (bacteria and fungi), but significant antibacterial activity was observed against *Klebsiella pneumoniae* and *Bacillus subtilis* (Rahman *et al.*, 2017) [42].

The ethyl acetate extract of the *Arthrinium* sp. MFLUCC16-1053 showed activity against both gram-positive and gram-negative bacteria. Specifically, the minimum inhibitory concentration against *Staphylococcus aureus* and *Escherichia coli* was 31.25 and 7.81 µg/mL, respectively. In addition, the crude extract showed highest antioxidant activity in 2, 2-diphenyl-1-picrylhydrazyl scavenging at IC₅₀ value of 28.47 µg/mL. Gas chromatography-mass spectrometry analysis revealed that the extract of the *Arthrinium* sp. MFLUCC16-1053 contains various antibacterial and antioxidant compounds β -cyclocitral, 3E-

cembrene A, laurenan-2-one, sclareol, 2Z, 6E-farnesol, cembrene, β -isocomene, and γ -curcumene. The fungus *Arthrinium* sp. MFLUCC16-1053 was also identified by molecular and phylogenetic methods (Acharavadee and Patcharee, 2018) [11].

Research was carried out on antibacterial activities of endophytic bacteria isolated from *Taxus brevifolia* against foodborne pathogenic bacteria: *Bacillus cereus*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Escherichia coli* and *Salmonella Typhimurium*. The number of endophytic bacteria isolated from seed (TbS) was 8, from fleshy part of fruit (TbFI) were ten and from leaves (TbL) were 22. TbFI-10 showed the highest antibacterial activity against all the bacteria and was identified as *Paenibacillus kribbensis* (Pk). An ethyl acetate extract of Pk- TbFI-10 possess antibacterial activity against the five foodborne pathogenic bacteria, with zones of inhibition from 15.71± 2.85 to 13.01± 2.12 mm (Islam *et al.*, 2018) [27].

Including tamarind pulp and leaf promoted digestibility of nutrients, and consequently the growth performance, in fish. Fish were fed with test diets fortified with 0.0% (positive control), 2 g oxytetracycline kg⁻¹ diet (negative control) and four varying levels (5, 10, 15, 20 g.kg⁻¹ diets) each of tamarind pulp or leaf meal at 3% body weight daily for 84 days. Fortification of the diets with tamarind significantly enhanced ($p \leq 0.05$) weight gain, specific growth rate, feed conversion ratio, nitrogen metabolism and survival rate, with the best performance at 20 g pulp and 10 g leaf (Olarinke *et al.*, 2018) [39].

Conclusion

Plant-based products have been used for medicinal and therapeutic purposes since the dawn of history. The use of plants as medicines has involved the isolation of active compounds. Isolation and characterisation of pharmacologically active compounds from medicinal plants is continuing even today. All the plants have mutualistic internal endophytic fungi or bacteria without causing any apparent symptoms in the host. Endophytes are a poorly investigated group of microorganisms capable of synthesizing bioactive compounds that can be used to combat numerous pathogens. These have been dependable sources of bioactive and chemically novel compounds and have proven useful for drug discovery. Biotransformation, methods have a wide range of uses, particularly in the production of numerous bioactive compounds, as antimicrobial (vanillin, essential oils), antifungal and antiviral (alkaloids), antioxidant (eugenol), anti-inflammatory (cineole) etc. Moreover, endophytes are good candidate for plant growth promotion in various crops through their multiple effects on plants like phytohormone production, nutrient absorption, and tolerance to biotic and abiotic stress. It is imperative to review and highlight the previous successes, ongoing research and latest developments in research associated with endophytic microorganisms to draw the attention of the research community toward this emerging field and possible exploitation of the available sources for their therapeutic uses in various fields, such as the medical, pharmaceutical, food and cosmetics.

Future perspective

Studies could be conducted to find out the mechanism of action of endophytic bacteria showing antibacterial activity.

Antibacterial activity of endophytic bacteria could be screened against other pathogenic organisms. Studies could be conducted to find out the other pharmacological actions of endophytic bacteria apart from antibacterial activity. Other plants could be screened for endophytic bacteria based on their historic therapeutic importance, climatic adversity etc.

References

1. Acharavadee P, Patcharee P. Antibacterial secondary metabolites from an endophytic fungus, *Arthrinium* sp. MFUCC16-1053 isolated from *Zingiber cassumunar*. International Journal on Fungal Biology. 2018;9(4):264-272.
2. Alloui N, Chafai S, Alloui MN. Effect of probiotic feed additives on broiler chickens' health and performance: an endophytic bacterium isolated from *Neesia altissima*. Journal of Microbiology. 2012;55(1):289-295.
3. Aly AH, Debbab A, Proksch P. Fungal endophytes: unique plant inhabitants with great promises. Applied Journal of Microbiology and Biotechnology. 2011;90:1829-1845.
4. Anjum N, Chandra R. Endophytic bacteria: Optimization of isolation procedure from various medicinal plants and their preliminary characterization. Asian Journal of Pharmaceutical and Clinical Research. 2015;8(4):233-238.
5. Aravamutham N, Kumar G, Karthik L, Bhaskara Rao KV. *In vitro* antagonistic activity of against multidrug-resistant bacteria. Pharmacology Online. 2010;2:507-551.
6. Arunachalam C, Gayathri P. Studies on bioprospecting of endophytic bacteria from the medicinal plant *Andrographis paniculata* for their antimicrobial activity and antibiotic susceptibility pattern. International Journal of Current Pharmaceutical Research. 2010;2(4):63-68.
7. Beiranvand M, Amin M, Hashemi A, Romani B, Yaghoubi S, Sadeghi P. Antimicrobial activity of endophytic bacterial populations isolated from medicinal plants of Iran. Iranian Journal of Microbiology. 2017;9(1):11-18.
8. Beneduzi A, Moreira F, Costa PB, Vargas LK, Lisboa BB, Favreto R, Baldani JI, Passaglia LMP. Diversity and plant growth-promoting evaluation abilities of bacteria isolated from sugarcane cultivated in the south of Brazil. Applied Soil Ecology. 2013;4:94-104.
9. Bhoonobong A, Sawaditang S, Sodngam S, Mongkolthanaruk W. Characterization of endophytic bacteria *Bacillus amyloliquefaciens* for antimicrobial agent's production. International Journal on Biological and Life Science. 2012;40:6-11.
10. Bibi F, Ullah I, Alvi SA, Baksh SA, Yasir M, Al-Ghamdi AAK, Azhar EI. Isolation, diversity, and biotechnological potential of rhizo and endophytic bacteria associated with mangrove plants from Saudi Arabia. Genetics and Molecular Research. 2017;6(2):1-12.
11. Brader G, Compant S, Mitter B, Trognitz F, Sessitsch A. Metabolic potential of endophytic bacteria. Current Opinion in Biotechnology. 2014;27:30-37. doi: 10.1016/j.copbio.2013.09.012
12. Christina A, Christopher V, Bhore S. Endophytic bacteria as a source of novel antibiotics. International Journal of Pharmacy and Pharmaceutical Sciences. 2013;7(13):11-16.
13. Compant S, Clement C, Sessitsch A. Colonization of plant growth-promoting bacteria in the rhizo and endosphere of plants: Importance, mechanisms involved and future prospects. Soil Biology and Biochemistry. 2010;42:669-678.
14. Conti R, Chagas FO, Caraballo-Rodriguez AM, Melo WG, do Nascimento AM, Cavalcanti BC, et al. Endophytic actinobacteria from the Brazilian medicinal plant *Lychnophora ericoides* Mart. and the biological potential of their secondary metabolites. Chemistry and Biodiversity. 2016;13:727-736. doi: 10.1002/cbdv.201500225
15. Costa OEL, Queiroz MV, Borges AC, Moraes AC, Araújo FE. Isolation and characterization of endophytic bacteria isolated from the leaves of the common bean (*Phaseolus vulgaris*). Brazilian Journal of Microbiology. 2012;43(4):1562-1575.
16. Das G, Patra JK, Baek K. Antibacterial properties of endophytic bacteria isolated from a fern species *Equisetum arvense* against foodborne pathogenic bacteria *Staphylococcus aureus* and *Escherichia coli* O157. Journal of Mycology. 2016;14(1):1-9.
17. Denise K, Zinniel P, Lambrecht H, Zhengyu F, Daniel K, Phyllis H, et al. Isolation and characterization of endophytic bacteria from crops. Applied and Environmental Microbiology. 2002;68(5):2198-2208.
18. Ding L, Munch J, Goerls H, Maier A, Fiebig HH, Lin WH, et al. Xiamycin, a pentacyclic indolosesquiterpene with selective anti-HIV activity from a bacterial mangrove endophyte. Bioorganic and Medicinal Chemistry Letters. 2010;20:6685-6687. doi: 10.1016/j.bmcl.2010.09.010
19. El-Deeb B, Fayez K, Gherbawy Y. Isolation and characterization of endophytic bacteria from *Plectranthus tenuiflorus*, a medicinal plant in Saudi Arabia desert, and their antimicrobial activities. Journal of Plant Interactions. 2013;8(1):56-64.
20. Gao Y, Liu Q, Zang P, Li X, Ji Q, He Z, et al. An endophytic bacterium isolated from *Panax ginseng* C.A. Meyer enhances growth, reduces morbidity, and stimulates ginsenoside biosynthesis. Phytochemistry Letters. 2015;11:132-138. doi: 10.1016/j.phytol.2014.12.007
21. Gayathri P, Muralikrishnan V. Antibacterial activity of endophytic bacteria isolated from mangrove plants. International Journal of Research in Pharmaceutical and Nano Sciences. 2013;2(4):530-535.
22. Ghiasvand M, Makhdoomi A, Matin MM, Vaezi J. Exploring the bioactive compounds from endophytic bacteria of a medicinal plant: *Ephedra foliata* (Ephedrales: Ephedraceae). Advances in Traditional Medicine. 2019;20:61-70. doi: 10.1007/s13596-019-00410-z
23. Golinska P, Wypij M, Agarkar G, Rathod D, Dahm H, Rai M. Endophytic actinobacteria of medicinal plants: diversity and bioactivity. Antonie van Leeuwenhoek. 2015;108(2):267-289. doi: 10.1007/s10482-015-0502-7
24. Guo B, Dai JR, Huang Y, Leong C, Ong W, Carte BK. Cytonic acids A and B: novel tridepside inhibitors of hCMV protease from the endophytic fungus *Cytospora* species. Journal of Natural Products. 2000;63:602-604.

25. Hardoim PR, Van Overbeek LS, Berg G, Pirttilä AM, Compant S, Campisano A, et al. The hidden world within plants: ecological and evolutionary considerations for defining functioning of microbial endophytes. *Microbiology and Molecular Biology Reviews*. 2015;79:293-320.
26. Ipsita D, Mrunmaya KP, Chandi CR, Kumaananda T. Bioactivities of bacterial endophytes isolated from leaf tissues of *Hyptis suaveolens* against some clinically significant pathogens. *Journal of Applied Pharmaceutical Science*. 2017;7(8):131-136.
27. Islam SA, Math R, Kim J, Yun M, Cho J, Kim E, et al. Effect of plant age on endophytic bacterial diversity of balloon flower (*Platycodon grandiflorum*) root and their antimicrobial activities. *Current Microbiology*. 2018;61:346-356.
28. Ji SH, Gururami MA, Chun SC. Isolation and characterization of plant growth-promoting endophytic diazotrophic bacteria from Korean rice cultivars. *Microbiological Research*. 2014;169:83-98.
29. Jia D, Xiao J, Dang SW, Yan QH. Isolation and identification of endophytic bacteria from root tissues of *Salvia miltiorrhiza* and determination of their bioactivities. *Annals of Microbiology*. 2013;63:1501-1512.
30. Kaaria P, Matiru V, Ndungu M. Antimicrobial activities of secondary metabolites produced by endophytic bacteria from selected indigenous Kenyan plants. *African Journal of Microbiology Research*. 2012;6(45):7253-7258.
31. Khanam B, Chandra R. Isolation and identification of endophytic bacteria producing bright red pigment from the dye yielding plant *Beta vulgaris*. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2015;7(5):220-4.
32. Krishnan P, Bhat R, Kush A, Ravikumar P. Isolation and functional characterization of bacterial endophytes from *Carica papaya* fruits. *Journal of Applied Microbiology*. 2012;113:308-17.
33. Kukla M, Plociniczak T, Seget P. Diversity of endophytic bacteria in *Lotium perenne* and their potential to degrade petroleum hydrocarbons and promote plant growth. *Chemosphere*. 2014;13:12-3.
34. Kumar AG, Antony RA, Kannan RV. Exploration of endophytic microorganisms from selected medicinal plants and their control potential to multi-drug resistant pathogens. *Journal of Medicinal Plants Studies*. 2015;3(2):49-57.
35. Li E, Jiang L, Guo L, Zhang H, Che Y. Pestalochlorides A-C, antifungal metabolites from the plant endophytic fungus *Pestalotiopsis adusta*. *Bioorganic and Medicinal Chemistry*. 2008;16:7894-9.
36. Liu Y, Liu W, Liang Z. Endophytic bacteria from *Pinellia ternata*, a new source of purine alkaloids and bacterial manure. *Pharmaceutical Biology*. 2015;53:1545-8. doi: 10.3109/13880209.2015.1016580.
37. Lodewyckx C, Vangronsveld J, Porteous F, Moore ERB, Taghavi S, Mezgey M, et al. Endophytic bacteria and their potential applications. *Critical Reviews in Plant Sciences*. 2002;21:583-606.
38. Merrett GLB. Tackling antibiotic resistance for greater global health security. Chatham House. 2013.
39. Olarinke V, Adeniyi F, Olaifa E, Benjamin E. Growth performance and nutrient digestibility of *Clarias gariepinus* fed diets fortified with *Tamarindus indica* pulp and leaf meal. *Journal of Ethnopharmacology*. 2018;31:17-31.
40. Pittayakhajonwut P, Suvannakad R, Thienhirun S, Prabpai S, Kongsaree P, Tanticharoen M. An antiherpes simplex virus-type 1 agent from *Xylaria mellisii* BCC 1005. *Tetrahedron Letters*. 2005;46:1341-4.
41. Prasad MP, Dagar S. Identification and characterization of endophytic bacteria from fruits like Avocado and Black grapes. *International Journal of Current Microbiology and Applied Sciences*. 2014;3(8):937-47.
42. Rahman L, Shinwari ZK, Iqar I, Rahman L, Tanveer F. An assessment on the role of endophytic microbes in the therapeutic potential of *Fagonia indica*. *Annals of Clinical Microbiology and Antimicrobials*. 2017;16:1-12.
43. Rekha M, Gupta P, Kale R, Madhuri L, Rath N, Jadhav P. Isolation, characterization and identification of endophytic bacteria by 16S rRNA partial sequencing technique from roots and leaves of *Prosopis cineraria* plant. *Asian Journal of Plant Science and Research*. 2015;5(6):36-43.
44. Ritu S, Kumar A, Yadav A, Giri DD, Singh PK, Pandey KD. Isolation and characterization of bacterial endophytes of *Curcuma longa*. *Biotechnology*. 2016;6:60.
45. Roy S, Banerjee D. Isolation of antimicrobial compound by endophytic bacteria from *Vinca rosea*. *International Journal of Current Research*. 2010;5:47-51.
46. Sasaki T, Igarashi Y, Saito N, Furumai T. Cedarmycins A and B, new antimicrobial antibiotics from *Streptomyces* sp. TP-A0456. *Journal of Antibiotics*. 2001;54:567-72. doi: 10.7164/antibiotics.54.567.
47. Yalew ST. Review on antibiotic resistance: Resistance mechanisms, methods of detection and its controlling strategies. *Biomedical Journal of Scientific & Technical Research*. 2020;24(5).
48. Singh R, Dubey AK. Diversity and applications of endophytic actinobacteria of plants in special and other ecological niches. *Frontiers in Microbiology*. 2018;9:1767. doi: 10.3389/fmicb.2018.01767.
49. Soman S. Studies on antibacterial activity of endophytic bacteria isolated from *Acacia nilotica*, *Acacia catechu* and *Acacia auriculiformis* [M.V.Sc. thesis]. Nanaji Deshmukh Veterinary Science University, Jabalpur; 2018.
50. Song JH. What's new on the antimicrobial horizon? *International Journal of Antimicrobial Agents*. 2008;32.
51. Strobel GA, Daisy B. Bioprospecting for microbial endophytes and their natural products. *Microbiology and Molecular Biology Reviews*. 2003;67:491-502.
52. Sturz AV, Nowak J. Endophytic communities of rhizobacteria and the strategies required to create yield enhancing association with crops. *Applied Soil Ecology*. 2000;15:182-90.
53. Suhandono S, Kartika MK, Aditiawati P. Isolation and molecular identification of endophytic bacteria from rambutan fruits (*Nephelium lappaceum*) cultivar Binjai. *Hayati Journal of Biosciences*. 2016;23:39-44.
54. Sun H, He Y, Xiao Q, Ye R, Tian Y. Isolation, characterization and antimicrobial activity of endophytic bacteria from *Polygonum cuspidatum*.

- African Journal of Microbiological Research. 2013;7(16):1496-504.
55. Sunkar S, Nachiyar V. Isolation and characterization of an endophytic bacterium from *Brassica oleracea* with potential enzyme and antibacterial activity. Asian Journal of Pharmaceutical and Clinical Research. 2013;6(2):183-187.
56. Tan RX, Zou WX. Endophytes: A rich source of functional metabolites. Natural Product Reports. 2001;18:448-59.
57. Tiwari R, Kalra A, Darokar MP, Chandra M, Aggarwal N, Singh AK, et al. Endophytic bacteria from *Ocimum sanctum* and their yield-enhancing capabilities. Current Microbiology. 2010;60:167-171. doi: 10.1007/s00284-009-9520-x.
58. Triratna S, Puspita L, Yulin L. Population and diversity of endophytic bacteria associated with medicinal plant *Curcuma zedoaria*. Microbiology Indonesia. 2014;8(2):65-72.
59. Verma SK, Kharwar RN, White JF. The role of seed-vectored endophytes in seedling development and establishment. Symbiosis. 2019;78:107-113. doi: 10.1007/s13199-019-00619-1.
60. Yu HL, Zhang L, Li C, Zheng, Guo L. Recent developments and future prospects of antimicrobial metabolites produced by endophytes. Microbiological Research. 2010;165:437-449.