Chapter 8
Endophytic Bacteria Associated with Medicinal Plants: The Treasure Trove of Antimicrobial Compounds

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Abstract Medicinal plants are recognized as prolific producer of bioactive compounds against an array of diseases. However, attention has been currently directed towards endophytic bacteria present inter- and/or intracellularly within host medicinal plants through symbiotic or parasitic interactions. They are the storehouse of wide variety of novel secondary metabolites that can serve as an excellent source of antimicrobial drugs. Hence, there is more opportunity to discover novel antimicrobial compounds from endophytic bacteria. In this scenario, it is of prime importance to focus research on the exploration of endophytic bacteria from medicinal plants and their utilization for the discovery of drug. Keeping on these importances, the intent of this chapter is to provide insights of the occurrence of medicinal plants with antimicrobial activities, exploration of medicinal plants for the isolation of endophytic bacteria and their potential to produce antimicrobial compounds against various pathogenic diseases.

Keywords Endophytic bacteria · Medicinal plants · Antimicrobial activity

8.1 Introduction

With increasing appearance of infectious pathogens, it is a big challenge to find new drugs where natural products have proved to be an attractive resource. Among the natural products, medicinal plants are of major importance. These plants are traditionally used worldwide as remedies for the treatment of various diseases which is due to the bioprospection of secondary metabolites produced by those plants (Egamberdieva et al. 2017). Especially, in developing countries, 80% of people rely on herbal drugs for primary healthcare (Chen et al. 2016). In comparison to modern

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synthetic drugs, these herbal medicines are economical and considerably safer. More than half of the pharmaceuticals being used today were derived from these natural products. However, due to major use of medicinal plants for drug discovery, it was reported that many of the medicinal plants are in endangered status or even in the verge of extinction; hence focus has turned towards endophytic bacteria which reside inter- and/or intracellularly within medicinal plants and proven to be the potential source of drug discovery (Venugopalan and Srivastava 2015). They form interactions with host plants ranging from mutualism to parasitism (Strobel 2002). The population structure of endophytic bacteria is strongly affected by genetic background of host plants, its fitness, ecological habitats where the plants live and soil nutrients (Jia et al. 2016). Consequently, it is also hypothesized that endophytic bacteria produce the same type of secondary metabolites as that of host plant species (Qin et al. 2011). Endophytic bacteria produce secondary metabolites of diverse pharmacological activities to protect host plant species from pathogens, to increase ability of plants to tolerate various types of abiotic and biotic stresses, improved nutrient acquisition, and plant growth promotion (Elsebai et al. 2014). Unexpectedly, it was observed that endophytic bacteria are more potential source of metabolites with high therapeutic potential than that of plants (Gouda et al. 2016). Additionally, microorganisms can be easily manipulated both physicochemically and genetically to increase yields of desired natural products (Elsebai et al. 2014).

However, among the different medicinal plants of the world, only a limited percentage were explored till now for endophytic bacterial population and their capacity to produce compounds with significant bioactivities. Consequently, the opportunity to discover new and fascinating endophytic bacteria among the myriad of medicinal plants is also exceptionally incredible. Hence, it is imperative to review the previous successes, ongoing research and latest developments in research associated with the presence of medicinal plants with antimicrobial activities, exploration of medicinal plants for the isolation of endophytic bacteria and their potential to produce antimicrobial compounds.

8.2 Medicinal Plants with Antimicrobial Activity

The plants containing useful concentration of medically active substances are known as medicinal plants. Such plants are traditionally utilized since ancient times for the treatment of different health problems (Nostro et al. 2000). As evidence from archaeological findings, clay tablets and ancient manuscripts, the peoples of Egypt, India, Greek, Roman, Summaria, Babylon and China developed their respective system of medicines from plants (Yaniv 2014). The medicinal properties of those plants are due to their capacity to synthesize a vast array of secondary metabolites such as alkaloids, resins, glycosides, triterpene alcohols, flavonoids, crotenoides and phenolic acids (Nascimento et al. 2000; Ramesh and Okigbo 2008). Mostly, medicinal plants are distributed in mega biodiversity countries of the world where India (which is considered as ‘herbarium of world’) and China containing utmost

numbers of medicinal plants, followed by Colombia, South Africa, the United States and other 16 countries (Chen et al. 2016). Most of the medicinal plants are flowering plants comprising of 33% trees followed by herbs, shrubs, climbers and lower groups of plants (Nishteswar 2014) which are distributed into different families.

With the growing population of the world, the existence of multidrug-resistant antimicrobial compounds is being threatened to mankind. Hence, there is an urgent need to synthesize new drug with novel mechanism of action for new and remerging infections disease (Marasini et al. 2015). In search of novel drugs, scientists have found that medicinal plants are the suitable alternatives to pure pharmaceuticals and are a source of new antimicrobial agents with low toxicity and are also free from side effects caused by synthetic chemicals (Khan et al. 2013). In search of medicinal plants having antimicrobial properties, it may be highly imperative to accumulate knowledge of traditional medicines. It has been reported that about 60–80% of populations in the developing countries use traditional medicine which were derived from medicinal plants (Chen et al. 2016). In recent years, various investigations of traditional medicinal plants have been led in different countries which have provided the world with many of clinical drugs of today (Table 8.1).

Table 8.1 Traditional uses of medicinal plant species with their taxonomic classification

Plant species	Family	Parts used	Medicinal/traditional uses	References
Bidens pilosa	Asteraceae	Root, leaf, seed	Antibacterial	Rojas et al. (2006)
Jacaranda mimosifolia	Bignoniaceae	Root, bark	Treatment of syphilis	
Piper pulchrum	Piperaceae	Whole plant	Treatment of haemorrhagic venom effect from snakebite and antidote for snakebite	
Bixa orellana	Bixaceae	Leaf and seed	Treatment of various diseases	
Cecropia peltata	Urticaceae	Leaf	Treatment of asthma and rheumatism	
Cinchona officinalis	Rubiaceae	Bark	Treatment of bloating, fullness and other stomach problems	
Gliricidia sepium	Fabaceae	Whole plant	Treatment of colds, cough, fever, headache	
Justicia secunda	Acanthaceae	Leaf and stem	Treatment of anaemia, cough, cold, fever, amenorrhoea	
Spilanthes americana	Asteraceae	Whole plant	Antibacterial	
Hemidesmus indicus	Apocynaceae	Root	Antibacterial	Kumar et al. (2007)
Eclipta alba	Asteraceae	Whole plant	Treatment of cough, indigestion, toothache	

(continued)

Table 8.1 (continued)

Plant species	Family	Parts used	Medicinal/traditional uses	References
Coscinium fenestratum	Menispermaceae	Stem	Antimicrobial, antidiabetic, anti-inflammatory	
Cucurbita pepo	Cucurbitaceae	Fruit and seed	Anti-inflammatory, analgesic urinary disorders, antidiabetic, antioxidant	
Tephrosia purpurea	Fabaceae	Root	Treatment of diarrhoea, rheumatism, asthma	
Mentha piperita	Lamiaceae	Leaf	Treatment of colds, cough, nausea	
Pongamia pinnata	Fabaceae	Whole plant	Treatment of piles, skin diseases and wounds	
Symplocos racemosa	Symplocaceae	Bark, flower	Treatment of ulcer, skin disorder, bleeding disorder	
Euphorbia hirta	Euphorbiaceae	Whole plant	Antibacterial, antimalarial, antioxidant	
Tinospora cordifolia	Menispermaceae	Whole plant	Antiperiodic, antimicrobial, anti-inflammatory, antiallergic, antidiabetic	
Thespesia populnea	Malvaceae	Bark, fruit	Treatment of dysentery, diabetes, gonorrhoea	
Jasminum officinale	Oleaceae	Flower	Aphrodisiac, antiseptic, antidepressant, antispasmodic, analgesic	
Allium sativum	Amaryllidaceae	Bulb	Antibacterial	Ushimaru et al. (2007)
Zingiber officinale	Zingiberaceae	Rhizome	Antibacterial	
Caryophyllus aromaticus	Myrtaceae	Flower bud	Antibacterial	
Cymbopogon citratus	Poaceae	Leaf	Antibacterial	
Mikania glomerata	Asteraceae	Leaf	Antibacterial	
Psidium guajava	Myrtaceae	Leaf	Antibacterial	
Acacia pennivenia	Mimosaceae	Leaf	Used for women with mastitis	Mothana et al. (2009)
Acanthospermum hispidum	Astraceae	Leaf	Antibacterial	
Acridocarpus socotranus	Malpighiaceae	Stem and leaf	Treatment of headaches, paralysis and muscle or tendon pain	
Aloe perryi	Aloaceae	Root	To treat stomach problems, constipation, malaria, wounds, burns	
Ballochia atro-virgata	Acanthaceae	Stem and leaf	Antibacterial	

(continued)

Table 8.1 (continued)

Plant species	Family	Parts used	Medicinal/traditional uses	References
Blepharis spiculifolia	Acanthaceae	Leaf and stem	Antibacterial	
Boswellia dioscorides	Burseraceae	Bark	To treat common cold, bronchitis, asthma and rheumatism	
Boswellia socotrana	Burseraceae	Bark	To treat common cold, bronchitis, asthma and rheumatism	
Capparis cartilaginea	Capparaceae	Leaf	To treat itching, shortness of breath, head cold, tumour	
Commiphora ornifolia	Burseraceae	Bark	Antiseptic, to treat diarrhoea, dysentery	
Corchorus erodioides	Tiliaceae	Flower and leaf	Diuretic and urinary tract infections	
Croton socotranus	Euphorbiaceae	Fruit and leaf	For wounds	
Euclea divinorum	Ebenaceae	Root	For oral care, toothache	
Euphorbia socotrana	Euphorbiaceae	Leaf	For skin diseases and wounds	
Eureiandra balfourii	Cucurbitaceae	Leaf	Antibacterial	
Ficus cordata	Moraceae	Leaf	Antiseptic and for ulcers and wounds	
Glossonema revoili	Asclepiadaceae	Flower and leaf	Increase milk production in breastfeeding women	
Hibiscus noli-tangere	Malvaceae	Leaf and root	For snakebite and fever in children	
Hypoestes pubescens	Acanthaceae	Leaf	Fungal skin diseases and scabies	
Lannea transulta	Anacardiaceae	Leaf	Haemostatic for wounds and sores	
Leucas samhaensis	Labiatae	Leaf	For cough and cold	
Leucas virgata	Labiatae	Leaf	For persons with heartburn and indigestion	
Lycium sokotranum	Solanaceae	Leaf and stem	For stomach ailments	
Maerua angolensis	Capparaceae	Leaf	To treat fever, aches and general malaise	
Rhus thyrsiflora	Anacardiaceae	Fruit and leaf	To treat anorexia, general tonic, and for painful joints	
Teucrium sokotranum	Labiatae	Flower and leaf	As flavouring agent and for indigestion	
Zingiber officinale	Zingiberaceae	Rhizome	Analgesic, sedative, antipyretic and antibacterial	Sharma et al. (2009)

(continued)

Table 8.1 (continued)

Plant species	Family	Parts used	Medicinal/traditional uses	References
Cinnamomum cassia	Lauraceae	Bark	Antibacterial, circulatory, respiratory, uterotonic and stomachic	
Terminalia chebula	Combretaceae	Fruit	Laxative, stomachic, tonic and alternative	
Plantago ovata	Plataginaceae	Husk	Constipation, colitis, irritable bowel, cystitis	
Vachellia nilotica	Fabaceae	Leaf	Treating premature ejaculation	
Pimpinella anisum	Apiaceae	Seed	Antiseptic, digestive, galactagogue, pectoral, stimulant	
Ocimum sanctum	Laminaceae	Leaf	Antibacterial, cures cough, cold, skin diseases	
Azadirachta indica	Meliaceae	Fruit	Skin disease, blood disorder, antibacterial	
Phyllanthus fraternus	Euphorbiaceae	Leaf	Jaundice, liver disease, fever, genitourinary disease, oedema	
Coriandrum sativum	Apiaceae	Seed	Flatulence, colic, joint pain, antiseptic	
Abutilon indicum	Malvaceae	Stem	Demulcent, aphrodisiac, laxative, astringent and diuretic, analgesic	
Punica granatum	Lythraceae	Seed	Anthelminthic (esp. tapeworm), diarrhoea, dyspepsia	
Syzygium cumini	Myrtaceae	Bark	Astringent, stomachic, carminative, antiscorbutic, diuretic	
Cyperus scariosus	Cyperaceae	Root	Astringent, diaphoretic, desiccant, cordial and stomachic	
Andrographis paniculata	Acanthaceae	Bark	Laxative, antipyretic, antiperiodic, anti-inflammatory, antibacterial	
Mangifera indica	Anacardiaceae	Leaf	Supplement of sexual potency, antiallergic, hypoglycaemic and antidiabetic	
Achillea millefolium	Asteraceae	Flower	Analgesic, antidiarrheal, antiemetic, Anthelmintic	Frey and Meyers (2010)
Ipomoea pandurata	Convolvulaceae	Flower, leaf	Analgesic, cough, gastrointestinal	
Hieracium pilosella	Asteraceae	Flower, leaf, stem	Antidiarrheal	
Solidago canadensis	Asteraceae	Leaf	Analgesic, gastrointestinal, sedative	

(continued)

Table 8.1 (continued)

Plant species	Family	Parts used	Medicinal/traditional uses	References
Hesperis matronalis	Brassicaceae	Stem	Antibacterial	
Rosa multiflora	Rosaceae	Flower, leaf	Antibacterial	
Asphodelus tenuifolius	Liliaceae	Fruit	Diuretic agent, healing wound	Panghal et al. (2011)
Asparagus racemosus	Liliaceae	Root	Demulcent, diuretic, aphrodisiac, antiseptic antiparasitic, antitumor	
Balanites aegyptiaca	Balanitaceae	Fruit	To cure mouth ulcer, whooping cough, sleeping sickness and skin diseases	
Cordia dichotoma	Boraginaceae	Fruit	Anthelminthic, diuretic, purgative, useful in dry cough, for cure of jaundice	
Eclipta alba	Asteraceae	Whole plant	Alopecia, ringworm, hepatitis, jaundice	
Murraya koenigii	Rutaceae	Leaf, bark, root	Treatment of stomachache, stimulant, piles, influenza, rheumatism, traumatic injury	
Pedalium murex	Pedaliaceae	Fruit	Aphrodisiac, antiseptic, demulcent, diuretic	
Ricinus communis	Euphorbiaceae	Seed, fruit	Antidote, bactericide, expectorant, insecticide, larvicidal, laxative, purgative	
Trigonella foenum	Fabaceae	Leaf	Remedy for fever and swelling	
Piptadeniastum africana	Fabaceae	Leaf	Antibacterial	Assob et al. (2011)
Cissus aralioides	Vitaceae	Leaf	Antibacterial	
Hileria latifolia	Phytolaccaceae	Leaf	Antibacterial	
Phyllanthus muellerianus	Phyllanthaceae	Stem bark	Antibacterial	
Gladiolus gregasius	Iridaceae	Bulb	Antibacterial	
Aloe vera	Asphodelaceae	Whole plant	Antibacterial	Selvamohan et al. (2012)
Phyllanthus emblica	Phyllanthaceae	Whole plant	Antibacterial	
Phyllanthus niruri	Phyllanthaceae	Whole plant	Antibacterial	
Cynodon dactylon	Poaceae	Whole plant	Antibacterial	
Murrya koenigii	Rutaceae	Whole plant	Antibacterial	

(continued)

Table 8.1 (continued)

Plant species	Family	Parts used	Medicinal/traditional uses	References
Lawsonia inermis	Lythraceae	Whole plant	Antibacterial	
Adhatoda vasica	Acanthaceae	Whole plant	Treat asthma, bronchitis, tuberculosis and antibacterial	
Coscinium fenestratum	Menispermaceae	Stem	Antimicrobial, antidiabetic, anti-inflammatory	Kaewpiboon et al. (2012)
Sonneratia alba	Lythraceae	Leaf	Treat swellings and sprains	
Anacardium occidentale	Anacardiaceae	Leaf	To treat fever, malaria, toothache and gum problems	
Acacia karoo	Mimosoideae	Leaf, stem, bark	Mouth ulcers, oral thrush, diarrhoea,	Nielsen et al. (2012)
Erythrophleum lasianthum	Caesalpinioideae	Leaf, stem	Headaches, fever	
Salvia africana	Lamiaceae	Leaf	Colds, flu, bronchitis, abdominal and uterine trouble	
Curtisia dentate	Cornaceae	Leaf, stem	Stomach ailments, diarrhoea, blood purifier	
Ptaeroxylon obligun	Ptaeroxylaceae	Leaf, stem, bark	Snuff for headache, rheumatism, arthritis	
Hymenelobium petraeum	Fabaceae	Whole plant	Antibacterial	Oliveira et al. (2013)
Vatairea guianensis	Fabaceae	Bark, seed and leaf	Treatment of scabies, skin diseases	
Symphonia globulifera	Clusiaceae	Bark and leaf	To treat river blindness, coughs in children	
Lagerstroemia indica	Lythraceae	Leaf	Antibacterial	Chandra (2013)
Annona reticulata	Annonaceae	Leaf	Antibacterial	
Achyranthes aspera	Amaranthaceae	Leaf, stem	Antibacterial	Pandey et al. (2013)
Bergenia ciliata	Saxifragaceae	Root	Antibacterial	Khan et al. (2013)
Jasminum officinale	Oleaceae	Leaf	Antibacterial	
Santalum album	Santalaceae	Wood	Antibacterial	
Artocarpus integer	Moraceae	Stem, root, bark	Antibacterial	Dej-adisai et al. (2014)
Averrhoa bilimbi	Oxalidaceae	Juice	Antibacterial	
Citrus ichangensis	Rutaceae	Peel	Antibacterial	
Cudrania javanensis	Moraceae	Wood	Antibacterial	
Ficus racemosa	Moraceae	Wood	Antibacterial	

(continued)

Table 8.1 (continued)

Plant species	Family	Parts used	Medicinal/traditional uses	References
Hydnophytum formicarum	Rubiaceae	Root	Antibacterial	
Sauropus changiana	Euphorbiaceae	Leaf	Antibacterial	
Solanum ferox	Solanaceae	Branch	Antibacterial	
Bergenia ciliata	Saxifragaceae	Rhizome	It is used in washing ulcer, to cure backbone and in wound healing	
Punica granatum	Lythraceae	Fruit	It is used in piles, diarrhoea, dysentery, whooping cough	
Azadirachta indica	Meliaceae	Leaf	Antibacterial	Farjana et al. (2014)
Camellia sinensis	Theaceae	Leaf	Antibacterial	
Psidium guajava	Myrtaceae	Leaf	Antibacterial	
Calendula officinalis	Asteraceae	Leaf	Antibacterial	
Acorus calamus	Araceae	Rhizomes	Cough, respiratory tract infections, skin disease, toothache, dysentery	Marasini et al. (2015)
Adhatoda vasica	Acanthaceae	Leaves	Bronchitis, asthma, diarrhoea, dysentery, as anthelmintic	
Artemisia vulgaris	Compositae	Aerial parts	Antiseptic, diarrhoea, dysmenorrhea, asthma, as anthelmintic	
Asparagus racemosus	Liliaceae	Rhizome, stem	Urinary troubles, diarrhoea	
Centella asiatica	Umbelliferae	Whole plant	Urinary tract infection, leprosy, ulcers, indigestion	
Cinnamomum camphora	Lauraceae	Leaf, seed, bark	As antiseptic, bronchitis, bronchopneumonia, epilepsy	
Curcuma longa	Zingiberaceae	Rhizome	Antiseptic, cuts, wounds, as anthelmintic, jaundice, liver disorders	
Cuscuta reflexa	Cuscutaceae	Whole plant	Fever, stomachache, rheumatism, anthelmintic	
Cynodon dactylon	Poaceae	Whole plant	Cuts, wounds, indigestion, genitourinary disorders	
Eupatorium adenophorum	Compositae	Leaf	Antiseptic	
Ginkgo biloba	Ginkgoaceae	Leaf	Alzheimer's disease, as anticoldness, as antinumbness	
Psidium guajava	Myrtaceae	Leaf, bark	Diarrhoea, dysentery, cuts, wounds, piles, cholera	

(continued)

Table 8.1 (continued)

Plant species	Family	Parts used	Medicinal/traditional uses	References
Rauwolfia serpentina	Apocynaceae	Root	As antidysenteric, as antidote to snakebite, cuts, wounds and boils	
Swertia chirayita	Gentianaceae	Aerial part	Skin disease, eczema, as anthelmintic, as antidiarrheal, dyspepsia	
Corymbia intermedia	Myrtaceae	Leaf	For the treatment of wounds	Packer et al. (2015)
Lophostemon suaveolens	Myrtaceae	Leaf	Antiseptic purposes	
Syncarpia glomulifera	Myrtaceae	Leaf	Antiseptic purposes	
Aframomum corrorima	Zingiberaceae	Fruit	Antibacterial	Bacha et al. (2016)
Albizia schimperiana	Fabaceae	Root	Antibacterial	
Curcuma longa	Zingiberaceae	Rhizome	Antibacterial	
Erythrina brucei	Fabaceae	Stem, bark	Antibacterial	
Justicia schimperiana	Acanthaceae	Seed	Antibacterial	
Nigella sativa	Ranunculaceae	Seed	Antibacterial	
Ocimum sauve	Lamiaceae	Leaf	Antibacterial	
Vernonia amygdalina	Asteraceae	Leaf	Antibacterial	
Ferula songorica	Apiaceae	Root	Antioxidant, antiviral, antifungal	Liu et al. (2016)
Hypericum perforatum	Hypericaceae	Leaf	Antibacterial	Egamberdieva et al. (2017)
Teucrium polium	Lamiaceae	Leaf	Antibacterial	Hassan (2017)
Echinacea purpurea	Asteraceae	Root, leaf	Antibacterial	Maggini et al. (2017)

8.3 Endophytic Bacteria Associated with Medicinal Plants

Medicinal plants are the source of various bioactive compounds against different ailments for centuries, and association of bacteria have been proven to offer advantages to these plants with high therapeutic potentials (Gouda et al. 2016). Endophytes present in medicinal plants perhaps contribute in their metabolic pathways and produce analogous or novel bioactive compounds (Qin et al. 2011).

Endophytic bacteria are those which are present inter- and/or intracellularly within a plant species without causing any obvious negative harm to the host (Barman and Dkhar 2015). The existence of endophytes has been known for more than 125 years ago (Bacon and White 2000). In 1886, De Bary first introduced the term endophytes for microorganisms harbouring internal plant tissues (Stepniewska

and Kuzniar 2013). Since then, Galippe (1887), Henning and Villforth (1940), Carrol (1986), Petrini (1991), Hirsch and Braun (1992) and Hallmann et al. (1997) have defined endophytes in different ways (Stepniewska and Kuzniar 2013). It is generally accepted that medicinal plants with an ethnobotanical history may harbour greater number of endophytic microbiome. Virtually, all the medicinal plant species on earth are the hosts of one or more types of endophytic bacteria (Strobel and Daisy 2003). These inhere in the living tissues of the host plant in a variety of relationships ranging from symbiotic mutualism to parasitism (Strobel 2002). Hence, the presence of endophytes in a plant species is considered as a sign of a healthy plant system (Barman and Dkhar 2018). Endophytic bacteria are promising sources of various secondary metabolites including antibiotics, immunosuppressant, antiparasitics, antioxidants, anticancer agents, plant growth-stimulating metabolites and enzymes which have important roles in plant development and health. They can also protect the plants by providing the ability to defend against predators and help their hosts to adapt in different stress conditions for survival (Qin et al. 2011) (Table 8.2).

Table 8.2 Bacterial endobiome associated with medicinal plant species (period: 2007–2018)

Parts used	Host plant	Group	Identified endophytic microorganisms	Reference
Root	*Panax ginseng*	Bacilli	*Bacillus* sp.	Cho et al. (2007)
		Bacilli	*Bacillus sphaericus*	
		Actinobacteria	*Kocuria carniphila*	
		Proteobacteria	*Rahnella* sp.	
		Actinobacteria	*Microbacterium phyllosphaerae*	
		Gammaproteobacteria	*Pseudomonas* sp.	
		Actinobacteria	*Pseudoclavibacter helvolus*	
		Bacilli	*Bacillus megaterium*	
		Bacilli	*Bacillus* sp.	
		Bacilli	*Paenibacillus polymyxa*	
		Actinobacteria	*Microbacterium hydrocarbonoxydans*	
		Gammaproteobacteria	*Erwinia persicina*	
		Gammaproteobacteria	*Pseudomonas* sp.	
		Gammaproteobacteria	*Serratia plymuthica*	
		Actinobacteria	*Pseudoclavibacter helvolus*	
		Gammaproteobacteria	*Pseudomonas poae*	
		Gammaproteobacteria	*Pantoea ananatis*	
		Gammaproteobacteria	*Serratia plymuthica*	
		Actinobacteria	*Kocuria carniphila*	

(continued)

Table 8.2 (continued)

Parts used	Host plant	Group	Identified endophytic microorganisms	Reference
	Salvia miltiorrhiza	*Gammaproteobacteria*	*Pseudomonas brassicacearum* subsp. *neoaurantiaca*	Vendan et al. (2010)
		Alphaproteobacteria	*Agrobacterium tumefaciens*	
		Gammaproteobacteria	*Pseudomonas thivervalensis*	
		Gammaproteobacteria	*Pseudomonas frederiksbergensis*	
		Bacilli	*Bacillus aryabhattai*	
		Alphaproteobacteria	*Novosphingobium resinovorum*	
	Suaeda maritima	*Actinobacteria*	*Hoeflea suaedae* sp. nov	Chung et al. (2013)
	Origanum vulgare	*Gammaproteobacteria*	*Leclercia* sp.	Bafana (2013)
		Gammaproteobacteria	*Pseudomonas* sp.	
		Gammaproteobacteria	*Stenotrophomonas* sp.	
		Gammaproteobacteria	*Stenotrophomonas* sp.	
		Bacilli	*Bacillus* sp.	
		Bacilli	*Solibacillus* sp.	
		Bacilli	*Lysinibacillus* sp.	
	Cassia tora	Bacilli	*Bacillus subtilis*	Kumar et al. (2015)
		Alphaproteobacteria	*Agrobacterium tumefaciens*	
		Bacilli	*Bacillus* sp.	
		Gammaproteobacteria	*Pseudomonas putida*	
		Gammaproteobacteria	*Pseudomonas* sp.	
	Stachys lavandulifolia	*Actinobacteria*	*Amycolatopsis tolypophora*	Beiranvand et al. (2017)
	Physalis alkekengi	Bacilli	*Bacillus thuringiensis*	
	Allium schoenoprasum	Bacilli	*Bacillus aryabhattai*	
	Mentha pulegium	Bacilli	*Planomicrobium* sp.	
	Marrubium vulgare	*Actinobacteria*	*Actinoallomurus acacia*	
	Falcaria vulgaris	*Actinobacteria*	*Actinoallomurus oryzae*	
	Ocimum basilicum	Bacilli	*Bacillus polyfermenticus*	
	Chenopodium album	Bacilli	*Bacillus pumilus*	
	Gundelia tournefortii	Bacilli	*Bacillus*sp.	
	Achillea millefolium	Bacilli	*Staphylococcus* sp.	

(continued)

Table 8.2 (continued)

Parts used	Host plant	Group	Identified endophytic microorganisms	Reference
	Zataria multiflora	*Alphaproteobacteria*	*Azospirillum brasilense*	
	Chenopodium album	Bacilli	*Bacillus velezensis*	
	Lavandula angustifolia	Bacilli	*Planomicrobium chinense*	
	Cymbopogon olivieri	*Actinobacteria*	*Nocardia niigatensis*	
	Teucrium polium	*Gammaproteobacteria*	*Pseudomonas graminis*	
	Cucumis sativus	*Actinobacteria*	*Nocardia cyriacigeorgica*	
	Coriandrum sativum	*Actinobacteria*	*Microbacterium testaceum*	
Rhizome	*Zingiber officinale*	Bacilli	*Bacillus* sp.	Jasim et al. (2014)
		Gammaproteobacteria	*Pseudomonas* sp.	
		Gammaproteobacteria	*Stenotrophomonas* sp.	
		Bacilli	*Staphylococcus* sp.	
Stem	*Panax ginseng*	Bacilli	*Bacillus pseudomycoides*	Vendan et al. (2010)
		Actinobacteria	*Micrococcus luteus*	
		Bacilli	*Bacillus thuringiensis*	
		Bacilli	*Bacillus pumilus*	
		Bacilli	*Lysinibacillus sphaericus*	
		Bacilli	*Bacillus megaterium*	
		Bacilli	*Bacillus acidiceler*	
		Gammaproteobacteria	*Pseudomonas marginalis*	
		Gammaproteobacteria	*Stenotrophomonas maltophilia*	
		Alphaproteobacteria	*Agrobacterium tumefaciens*	
		Bacilli	*Paenibacillus glucanolyticus*	
		Bacilli	*Staphylococcus epidermidis*	
		Gammaproteobacteria	*Pectobacterium carotovorum*	
	Ipomoea batatas	*Gammaproteobacteria*	*Enterobacter* sp.	Khan and Doty (2009)
		Gammaproteobacteria	*Rahnella aquatilis*	
		Gammaproteobacteria	*Pseudomonas* sp.	
		Gammaproteobacteria	*Rhodanobacter terrae*	
		Gammaproteobacteria	*Stenotrophomonas maltophilia*	

(continued)

Table 8.2 (continued)

Parts used	Host plant	Group	Identified endophytic microorganisms	Reference
		Alphaproteobacteria	*Phyllobacterium myrsinacearum*	
		Gammaproteobacteria	*Xanthomonas* sp.	
	Piper nigrum	Bacilli	*Bacillus firmus*	Jasim et al. (2013)
		Bacilli	*Paenibacillus dendritiformis*	
		Gammaproteobacteria	*Pseudomonas* sp.	
		Betaproteobacteria	*Bordetella* sp.	
		Bacilli	*Bacillus* sp.	
		Gammaproteobacteria	*Stenotrophomonas* sp.	
	Alcea amcheri	*Actinobacteria*	*Dietzia cercidiphylli*	Beiranvand et al. (2017)
	Allium ursinum	*Alphaproteobacteria*	*Azorhizobium caulinodans*	
	Phasaeolous vulgaris	*Firmicutes*	*Bacillus* sp.	
	Rheum rhaponticum	*Actinobacteria*	*Streptomyces artemisiae*	
Leaf	*Aloe vera*	*Actinobacteria*	*Micrococcus aloeverae*	Prakash et al. (2014)
	Hylomecon japonica	*Alphaproteobacteria*	*Sphingobium endophyticus*	Zhu et al. (2015)
	Aloe vera	*Actinobacteria*	*Arthrobacter globiformis*	Beiranvand et al. (2017)
	Teucrium polium	*Firmicutes*	*Bacillus cereus*	Hassan(2017)
		Firmicutes	*Bacillus subtilis*	
Bulbil	*Dioscorea bulbifera* L.	*Actinobacteria*	*Streptomyces dioscori* sp. nov.	Wang et al. (2018)
Plant tissues	*Panax notoginseng*	Bacilli	*Bacillus amyloliquefaciens* subsp. *plantarum*	Ma et al. (2013)
		Bacilli	*Bacillus methylotrophicus*	
	Ferula songorica	*Alphaproteobacteria*	*Sphingomonas* sp.	Liu et al. (2016)
		Gammaproteobacteria	*Acinetobacter* sp.	
		Gammaproteobacteria	*Pseudomonas* sp.	
		Alphaproteobacteria	*Methylobacterium* sp.	
		Alphaproteobacteria	*Rhizobium* sp.	
		Alphaproteobacteria	*Paracoccus* sp.	
		Betaproteobacteria	*Ralstonia* sp.	
		Alphaproteobacteria	*Brevundimonas* sp.	
		Bacilli	*Paenibacillus* sp.	
		Bacilli	*Bacillus* sp.	

(continued)

Table 8.2 (continued)

Parts used	Host plant	Group	Identified endophytic microorganisms	Reference
		Actinobacteria	*Dietzia* sp.	
		Actinobacteria	*Nocardioides* sp.	
		Actinobacteria	*Saccharopolyspora* sp.	
		Actinobacteria	*Pseudonocardia* sp.	
		Actinobacteria	*Streptomyces* sp.	
		Actinobacteria	*Rhodococcus* sp.	
		Actinobacteria	*Promicromonospora* sp.	
		Actinobacteria	*Brevibacterium* sp.	
		Actinobacteria	*Micrococcus* sp.	
		Actinobacteria	*Arthrobacter* sp.	
		Actinobacteria	*Microbacterium* sp.	
	Glycyrrhiza uralensis	*Actinobacteria*	*Brevibacterium frigoritolerans*	Li et al. (2018)
		Bacilli	*Bacillus mojavensis*	
		Betaproteobacteria	*Achromobacter spanius*	
		Gammaproteobacteria	*Stenotrophomonas rhizophila*	
		Bacilli	*Bacillus aryabhattai*	

8.3.1 Origin and Localization of Endophytes

Endophytes are supposed to originate from the epiphytic bacterial communities of the rhizosphere, phylloplane, endophyte-infested seeds or planting materials as well as natural openings or wounds (Hallmann et al. 1997). They enter and colonize in plants mainly through emergence points of lateral roots, the zone of differentiation and elongation near the root tip, stomata, lenticels and broken trichome (Zinniel et al. 2002). Due to the lack of penetration structures, bacteria are unable to exert mechanical or physical forces to penetrate the epidermal cells. Bacteria normally enter intact plant tissue by invagination of the root hair cell wall, by penetration of the junction between root hair and adjacent epidermal cells or by secreting cell wall-degrading enzymes. Plants are autotrophic organisms which are capable for transforming light energy into chemical (carbonaceous) compounds. By releasing these photo-assimilated compounds from plant root into the rhizosphere, they can attract different microorganisms to become endophyte (Bais et al. 2004). On entering into plants, microorganisms spread inside the host plant species via intercellular spaces or conducting elements and ultimately reach the flowers or fruits. Endophytic microorganisms can also reach seed via vascular connections from the maternal plant, directly through gametes colonizing the resulting embryo and endosperm or through colonized shoot meristems which eventually rise to ovules and thus seeds (Truyens et al. 2015). Some bacteria can directly interact with seeds present in soil.

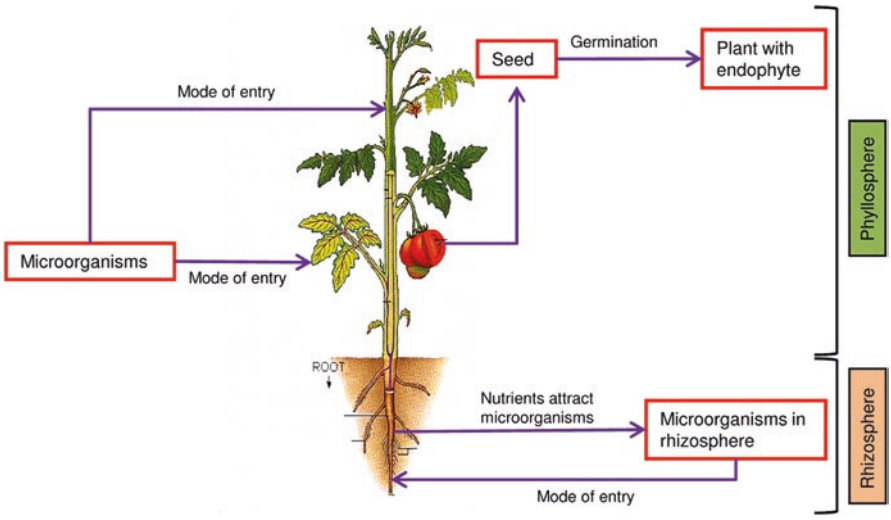

Fig. 8.1 Schematic representation of colonization routes of endophytic microorganisms

For that seed exudates released during imbibition and germination influence the bacterial population that can be supported in the spermosphere (Quadt-Hallman et al. 1997; Truyens et al. 2015) (Fig. 8.1).

The presence of endophytic bacterial colonization in tissues of plants can be documented based on microscopic study such as transmission electron microscopy (TEM), scanning electron microscopy (SEM) and confocal laser scanning microscopy by tagging them with autofluorescent protein (AFP) such as green fluorescent protein (GFP) and *Discosoma striata* red fluorescent protein (DsRed) (Gyaneshwar et al. 2001; Ryan et al. 2008; Thomas and Reddy 2013; Barman and Dkhar 2018). The colonization pattern and tracking of introduced endophytic microbes inside their niche can also be visualized by immunological methods on using monoclonal or polyclonal antibodies followed by ELISA, dot blot assay, tissue printing, immunogold labelling, fluorescent in situ hybridization (FISH), triphenyl tetrazolium chloride vital staining and fluorescence resonance energy transfer (FRET) (Hallmann and Kloepper 1996; Compant et al. 2011; Thomas 2011; Banik et al. 2016).

8.3.2 Culture-Dependent Analysis of Endophytic Bacteria

Isolation and characterization of endophytic bacteria have foremost importance to unearth antimicrobial compounds which mainly involve three steps - surface sterilization of collected plant parts, followed by fractionation of the plant material into

small pieces or pestled and homogenization of plant material in a mortar and lastly plating on suitable bacteriological media. Surface sterilization of plant parts is the important step to get rid of epiphytic microorganisms and to ensure that isolated strains are endophytes (Martinez-Klimova et al. 2017). It can be done by washing the collected plant parts in running tap water to remove soil debris followed by treating them with suitable sterilizing reagents to completely remove the epiphytic population. Commonly used disinfecting agents were 70% ethanol (EtOH), sodium hypochlorite (0.9–5.25%), mercuric chloride (0.1%), hydrogen peroxide, Triton-X-100 and Tween 80. It is necessary to treat the plant parts with the disinfecting agents for a suitable period of time to reduce their detrimental effect on plant tissue which leads to hamper the isolation of endophytic bacteria. After each treatment with the disinfecting agents, it is also necessary to wash the plant parts in sterile water to remove the agents (Cao et al. 2004; Kukkurainen et al. 2005; Qin et al. 2011; Jasim et al. 2014). To ensure the effectiveness of surface sterilization procedure, it's essential to use an aliquot of final sterile water from the mixture of surface-sterilized samples and sterile water followed by plating on isolation media (Barman and Dkhar 2015).

After surface sterilization, the plant parts have to plate on suitable isolation media followed by incubation for suitable time at desired temperature. The composition of media mainly depends on energy and nutrients requirement for their growth. Some of the classical media used for isolation of endophytic bacteria includes nutrient agar, Luria-Bertani agar, R2A agar and tryptic soy agar (Gagne-Bourgue et al. 2012; Zhang et al. 2014; Barman and Dkhar 2018). It is also important to note that on using a portion of autoclaved plant extracts of the host plant species to the growth media, isolation of endophytic bacterial population can be enhanced (Murphy et al. 2015).

To identify endophytic bacteria, various micromorphological, biochemical, and molecular techniques with appropriate bioinformatics tools are useful. *Alphaproteobacteria*, *Betaproteobacteria*, *Gammaproteobacteria*, *Actinobacteria*, and *Firmicutes* were the most common groups of endophytic bacteria isolated (Mendes et al. 2007; Ulrich et al. 2008; Vendan et al. 2010). Preliminary identification of bacterial isolates to the genus or species level can be done using various cultural, morphological, biochemical, physiological and chemotypic analyses (Shirling and Gottlieb 1966; Holt et al. 1994; Zhang et al. 2014). Though these aspects can identify bacteria up to genera, sometimes it is not adequate in itself to differentiate between many genera. The advent of molecular criteria for the characterization of bacteria has provided taxonomists with a set of reliable and reproducible tools for studying the systematics. Molecular identification of bacteria can be done by 16S rRNA gene amplification of genomic DNA. Percentage of G+C content of DNA and DNA/DNA-hybridization techniques are also useful tools for the identification of microbes. To characterize taxa at and below the rank of species, the DNA-DNA relatedness, molecular fingerprinting and phenotypic techniques are methods of choice (Zhang et al. 2014).

8.3.3 Culture-Independent Analysis of Endophytic Bacteria

Since culture-based techniques of analysing the diversity of endophytic bacterial community is dependent on various factors including cultivation media, growth conditions and plant tissue manipulation, hence, culture-independent method of analysing the diversity of endophytic bacterial community is more specific and replicable. It provides greater insights of endophytic bacterial community (Yang et al. 2017). In this aspect, metagenomics study with next-generation sequencing (NGS) technology, metatranscriptomics, metaproteomics and metaproteogenomics are widely used (Kaul et al. 2016). During the process, the genetic material has to be isolated from the plant samples followed by amplification of V3-V4 hypervariable region of the bacterial 16S rRNA gene using universal primers followed by sequencing on 454/Roche or Illumina/Solexa (HiSeq, MiSeq) platforms, and finally, the reads (short fragments of genomes obtained in sequencing) are assembled and annotated (Redford et al. 2010; Yang et al. 2017). These technologies can also explore the genes associated with the production of secondary metabolites which may be for plant growth promotion, biocontrol, nutrition and niche adaptation. It helps us to understand their role and mechanism in host plant interaction and protection (Tian et al. 2015).

8.4 Endophytic Bacteria for Their Antimicrobial Potential

Usually, the selection of bacteria for their antimicrobial activity can be evaluated by measuring the minimum inhibitory concentration (MIC) mainly by diffusion methods, dilution methods and bioautography on using the cell-free culture supernatant of the isolates or using the organic extracts of the isolates (Choma and Grzelak 2011). Diffusion methods including disc method, cylinder method and hole plate assay method are mainly used for determination of antimicrobial susceptibility of the test compound preferably of polar ones (Choma and Grzelak 2011), whereas dilution methods (agar dilution and tube assay) are frequently used to estimate the concentration of the test compound (both polar and nonpolar samples) which in the form of complex extracts or pure substances in the agar medium or in the broth suspension (Choma and Grzelak 2011). Bioautography (contact bioautography, immersion bioautography and direct bioautography) is another screening method for detection of antimicrobial activity which is more or less similar to agar diffusion method. The main advantage of this method is that it can be combined with thin-layer chromatography (TLC), high-performance thin-layer chromatography (HPTLC), overpressured-layer chromatography (OPLC) and planar electrochromatography (PEC) (Choma and Grzelak 2011).

Functional gene-based screening of the isolates for antimicrobial potential can be performed by PCR amplification of nonribosomal peptide synthetases (NRPS) and polyketide synthases (PKS) biosynthetic systems within the genomic sequences

of the isolates. Both of these systems are involved in the production of biologically active polyketide and peptide compounds including antibiotic having applications in medicine, agriculture and biochemical research (Amoutzias et al. 2008). Both of the systems are composed of multiple large peptides, each of them encoded by a variable number of modules. Each module can be further categorized into minimum three "domains" having special function (Amoutzias et al. 2008), out of which two are catalytical and one is carrier domain. As per current classification, PKSs have been grouped into type I, II and III (Hopwood 1997). Different PCR primers were used for the screening of NRPS and PKS systems including KS-BEF/KS-BER, A3F/A7R, K1F/M6R and K1F/K2R (Ayuso-Sacido and Genilloud 2005; Gonzalez et al. 2005).

8.5 Extraction and Characterization of Antimicrobial Compounds

After preliminary screening of the isolates for antimicrobial potentials as mentioned above, the next step is the fermentation and extraction of antimicrobial product. The culture medium selected for fermentation is mainly based on the species under investigation. After an optimum period of incubation, extraction can be performed. Preliminary low-polarity solvents extraction yields the more lipophilic components, while organic solvent extraction (methanol, ethanol and hexane) yields a larger spectrum of both nonpolar and polar materials. Traditionally extraction is mainly performed by Soxhlet extraction, maceration, percolation, turbo-extraction and sonication. However, due to some drawbacks, a number of new extraction methods have been developed including supercritical fluid extraction (SFE), pressurized liquid extraction (PLE), microwave-assisted extraction (MAE), solid-phase microextraction (SPME), ultrasound-assisted extraction (UAE), superheated liquid extraction and extraction with supercritical or subcritical water (Sticher 2008). Finally, active components can be isolated by an array of chromatographic methods depending on the solubility, volatility and stability of the compounds to be separated which are commonly considered as the bottleneck of the isolation process (Sticher 2008). Generally, precipitation-thin-layer chromatography, liquid preparation chromatography and column chromatography are used for the process of purification of the active compound (Hu et al. 2010). In the process of chromatography, selection of appropriate solvent system and packing material plays an important role. Silica, alumina, carbohydrates polyacrylamide and polystyrene are mainly used as stationary phases for purification.

Characterization of the purified active compound can be performed by a series of spectroscopic methods such as Fourier transform infrared spectrometer (FT-IR), UV-visible, nuclear magnetic resonance (NMR) and mass spectroscopy (MS) (Bhattacharjee et al. 2017). FT-IR spectrometer is used for characterization of functional groups of the drug molecule having diverse vibrational frequencies which

help to identify the chemical constituents and reveal the structural compounds (Altemimi et al. 2017). UV-visible spectroscopy is commonly used to identify the certain classes of compounds. NMR is related to the magnetic properties of certain atomic nuclei which enabled the researchers to find the positions of these nuclei in the molecule (Altemimi et al. 2017). MS is used to find the relative molecular mass and molecular formula of the compound with high accuracy based on the knowledge of relative abundance of a fragmented ion against the ratio of mass/charge of these ions (Fig. 8.2).

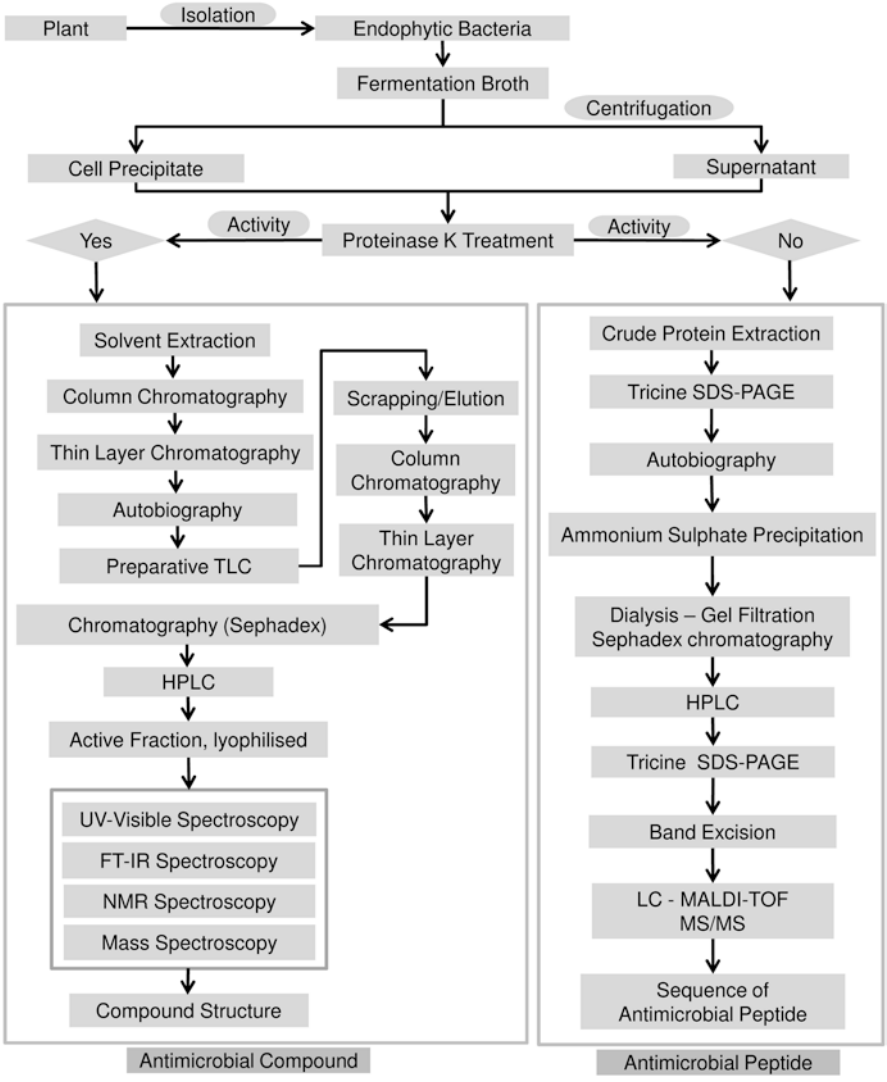

Fig. 8.2 Scheme representing the typical workflow for antimicrobial compounds from endophytic bacteria

8.6 Mechanism of Action of Antimicrobial Compounds

The antibiotics target bacterial cell death by inhibiting DNA synthesis, RNA synthesis, cell wall synthesis, protein synthesis and cell wall metabolism (Dzidic et al. 2008; Kohanski et al. 2010). To inhibit DNA synthesis, antimicrobial agents mainly quinolone class of antibiotics target on DNA gyrase (topoisomerase II) and topoisomerase IV. They bind to topoisomerase enzyme leading to DNA strand breakage. Similarly, to inhibit RNA synthesis, antimicrobial agents, for example, rifamycin can interfere with a DNA-directed RNA polymerase which is the main regulator of gene expression in prokaryotes. The inhibitor of protein synthesis is catagorized into the 50S inhibitors and 30S inhibitors. The 50S ribosome inhibitors (macrolide, lincosamide, streptogramin, amphenicol and oxazolidinone) can block initiation of protein translation or translocation of peptidyl-tRNAs which helps to inhibit the peptidyl transferase reaction that elongates the nascent peptide chain, whereas 30S ribosome inhibitors (tetracycline, aminoglycoside and aminocyclitol) can bind to 30S ribosome subunit and promoting tRNA mismatching which can result in protein mistranslation (Kohanski et al. 2010).

Bacterial cell wall mainly composed of peptidoglycan which is composed of peptide-linked β-(1–4)-N-acetyl hexosamine. Some of the antibiotics, for example, β-lactams, interfere with cell wall synthesis by inhibiting the peptide bond formation between the peptidoglycan units. Some of the antibiotics can inhibit peptidoglycan synthesis through binding with peptidoglycan units and by blocking transglycosylase and transpeptidase activity (Kohanski et al. 2010). Some of the antibiotics can also interfere with cell wall metabolism (Dzidic et al. 2008).

8.7 Antimicrobial Compounds Produced by Plant-Associated Bacteria

The human population is increasing with an alarming rate; ecosystems are deteriorating rapidly; and a variety of new types of health issues are popping up (Bhattacharjee et al. 2018). For instance, increase in number of drug-resistant bacteria is a cause of concern. In this perspective, bioprospecting for natural resources such as microorganisms, plants, algae and animals is the way for the discovery of new antibiotics (Martinez-Klimova et al. 2017). Among the natural sources of drug production, especially bacteria are the primary resource. However, for the discovery of drug, only a small percentage of bacteria have been explored (Bhattacharjee et al. 2018). Hence, it is extremely important to explore nature's hitherto untapped bacteria to achieve this objective. In this aspect, endophytic bacteria especially isolated from plants of ethnobotanical history are becoming the major trust area of research (Martinez-Klimova et al. 2017). The antimicrobial activity of endophytes was accounted for over 50 years when Smith (1957) isolated *Micromonospora* from the tomato plant which was reported to have antagonistic activity (Manikprabhu and Li

2015). Since then, endophytic bacteria were exploited to isolate various antimicrobial compounds.

Endophytic bacteria play an important role to produce a variety of antibiotics. They mainly produce those antibiotics to protect plants against stress, insects, pests and pathogenic microorganisms (Chandrakar and Gupta 2017). They have immense importance in various pharmaceutical industries, and they have agricultural applications also (Chandrakar and Gupta 2017). Among the antibiotic-producing endophytic bacteria, *Streptomyces* is the richest source of antibiotics, namely, Munumbicins A, Munumbicins B, Munumbicins C, Munumbicins D, Munumbicins E-4, Munumbicins E-5, Kakadumycin A, and Celastramycins A/B (Golinska et al. 2015). Some other bacterial species, including *Pseudomonas*, *Streptosporangium*, *Serratia*, *Bacillus*, *Azospirillum*, *Burkholderia* and *Azoarcus*, also subsidize a distinctive source of antibiotics. These antimicrobial compounds were found to be effective against a range of pathogenic bacteria, fungi and protozoa.

8.7.1 Munumbicins

Munumbicins A, B, C and D are some important antimicrobial peptides which showed activity against a wide spectrum of human as well as plant pathogenic fungi and bacteria and a *Plasmodium* sp. These antibiotics were obtained from *Streptomyces* sp. NRRL30562 which is an endophyte of *Kennedia nigricans.* All these antibiotics are peptides having common compositional features, and Munumbicins C and D represent a novel peptide where Munumbicins A and B are corresponding to actinomycin X2 and actinomycin D, respectively. All the Munumbicins A, B, C and D were found to be active against human-pathogenic bacterium and fungi *Pseudomonas syringae* and *Cryptococcus neoformans*, respectively, and some plant-pathogenic fungi *Pythium ultimum* and *Sclerotinia sclerotiorum* (Castillo et al. 2002). Also in the MIC test, Munumbicins A and C were effective against *Enterococcus faecalis* ATCC 51299, whereas Munumbicins C and D had bioactivity against a drug-sensitive strain of *Staphylococcus aureus* MH II and Munumbicin B against *Staphylococcus aureus* ATCC 33591. The Munumbicin B is of a special interest since it is active against multiple-drug-resistant *Mycobacterium tuberculosis* having IC_{50} value of 10 μgml^{-1}. Another outstanding activity of the Munumbicins was found against the malaria-causing pathogen *Plasmodium falciparum*. Though all the Munumbicins were active against *Plasmodium falciparum*, however, Munumbicins C and D were of special interest due to their low IC_{50} values.

Another two broad-spectrum antibiotics, namely, Munumbicins E-4 and Munumbicins E-5, were isolated from endophytic actinobacterium *Streptomyces* sp. NRRL3052 which was obtained from *Kennedia nigricans*, in the Northern Territory of Australia. Both the antibiotics were effective in the same range of biological activity against *Bacillus subtilis*, *Pythium ultimum* and *Staphylococcus aureus*. Munumbicin E-5 showed more effective than E-4 against *Burkholderia thailanden-*

sis; however, Munumbicin E-4 was more effective than E-5 against *Staphylococcus aureus* ATCC 29213 and *Staphylococcus aureus* 43000 (MRSA) (Castillo et al. 2006). The antimalarial activity of Munumbicins E-4 and E-5 is also reported to be double than that of chloroquine.

8.7.2 Kakadumycins

Streptomycete sp. (NRRL30566) an endophyte of *Grevillea pteridifolia* is the source of peptide antibiotics kakadumycins. The structure of the antibiotic is related to a quinoxaline antibiotic, echinomycin. Like echinomycin, kakadumycins also have same mode of action. It can preferentially inhibit DNA-directed enzymatic RNA synthesis along with it and also can inhibit protein synthesis and cell wall synthesis to some extent. The antibiotic is reported to have strong antimalarial and anti-*Bacillus anthracis* activities (Castillo et al. 2003).

8.7.3 Celastramycins

Celastramycins A and B were isolated from the *Streptomyces* sp. MaB-QuH-8 of the plant *Putterlickia retrospinosa*. Celastramycin A belongs to chloropyrrolo family of antibiotics, while Celastramycin B is an unusual chlorinated anthracyclinone metabolite (Fig. 8.3). On testing both the antibiotics against different pathogens, it was reported that Celastramycin A is more potent against multiresistant bacterial strain in comparison to Celastramycin B. Both Celastramycins A and B showed activity against *Mycobacterium vaccae* IMET 10670 and *Bacillus subtilis* ATCC 6633. In addition to that Celastramycin A was effective against some other pathogenic bacteria such as *Staphylococcus aureus* MRSA 134/93, *S. aureus* MR 994/93, *Enterococcus faecalis* V-r 1528, *Mycobacterium smegmatis* SG 98, *Mycobacterium aurum* SB 66 and *Mycobacterium fortuitum* (Pullen et al. 2002).

8.7.4 Coronamycins

Coronamycin is a novel group of peptide antibiotics which is active against various pythiaceous fungi, human fungal pathogen including *Pythium ultimum*, *Geotrichum candidum* and *Phytophthora cinnamomi*. The best bioactivity of Coronamycin was found against malarial parasite *Plasmodium falciparum* having IC_{50} values of 9 ± 7.3 ng ml^{-1}. It is produced by *Streptomyces* sp. which is an endophyte from an epiphytic vine, *Monstera* sp. Since this antibiotic is active against various pythiaceous fungi, it may be used for agricultural purposes (Ezra et al. 2004).

8.7.5 Xiamycins

Xiamycin A represents one of the novel pentacyclicindolosesquiterpene isolated from *Streptomyces* sp. strain HKI0595 from the stem segments of a mangrove tree, *Kandelia candel*. The research findings suggest that Xiamycin A has strong antimicrobial activities against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, *Mycobacterium vaccae*, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis* (Ding et al. 2011). Along with Xiamycin A, Ding et al. (2011) also isolated three new alkaloids, Xiamycin B, Indosespene and Sespenine, of which Indosespene and Sespenine have moderate or weak antimicrobial activities, respectively (Fig. 8.3).

8.7.6 Ecomycins

Ecomycin (Ecomycins A, Ecomycins B, Ecomycins C) is a novel family of lipopeptide antibiotics which was isolated from *Pseudomonas viridiflava*, an endophytic bacterium associated with grass species. Based on molecular weight and amino acid composition, Ecomycin A was found to be similar to Syringotoxin; however, Ecomycin B and C represented a unique set of related lipopeptides. The antibiotics showed bioactivity against human fungal pathogens including *Candida albicans* and *Cryptococcus neoformans* and some plant pathogenic fungi such as *Sclerotinia sclerotiorum*, *Fusarium oxysporum* and *Rhizoctonia solani*. The biological activities of the Ecomycin were found to be similar to Amphotericin B. However, since Amphotericin B is extremely toxic to human cells, hence, Ecomycin can be used as a suitable alternative to Amphotericin B (Miller et al. 1998).

8.7.7 Pseudomycin

Pseudomycin is an antibiotic which represent a family of lipopeptides and was reported from plant-associated *Pseudomonas syringae*. It was found to be active against an array of plant- and human-pathogenic fungi including *C. albicans*, *C. neoformans*, *Ceratocystis ulmi* and *Mycosphaerella fijiensis* (Harrison et al. 1991).

8.7.8 Efomycins

Streptomyces sp. BCC72023 isolated from *Oryza sativa* L. was found to be the source of three macrolides, Efomycin M, Efomycin G and Oxohygrolidin, and two polyethers, abierixin and 29-O-methylabierixin (Fig. 8.3). Efomycin M can inhibit

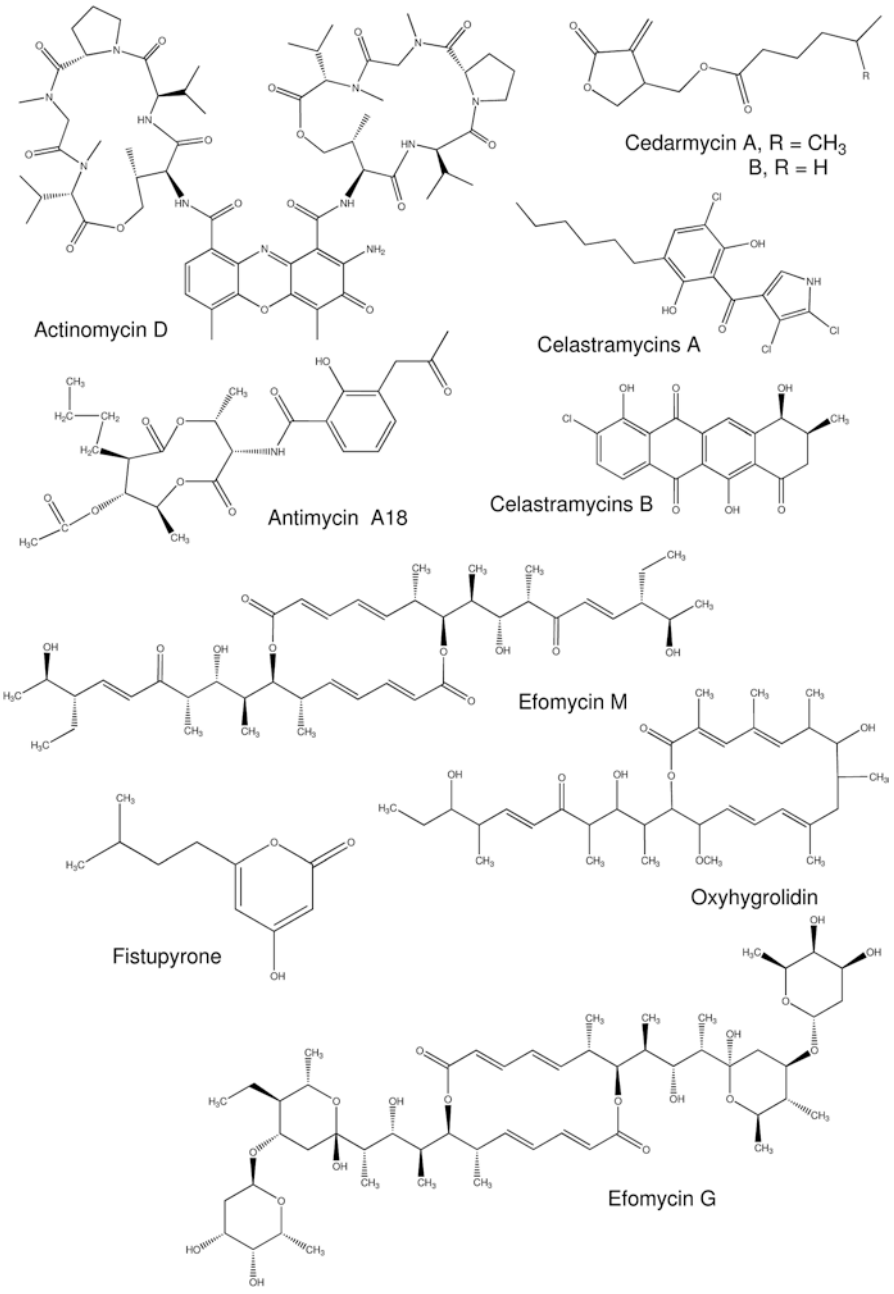

Fig. 8.3 Chemical structure of representative antimicrobial compounds obtained from endophytic bacteria

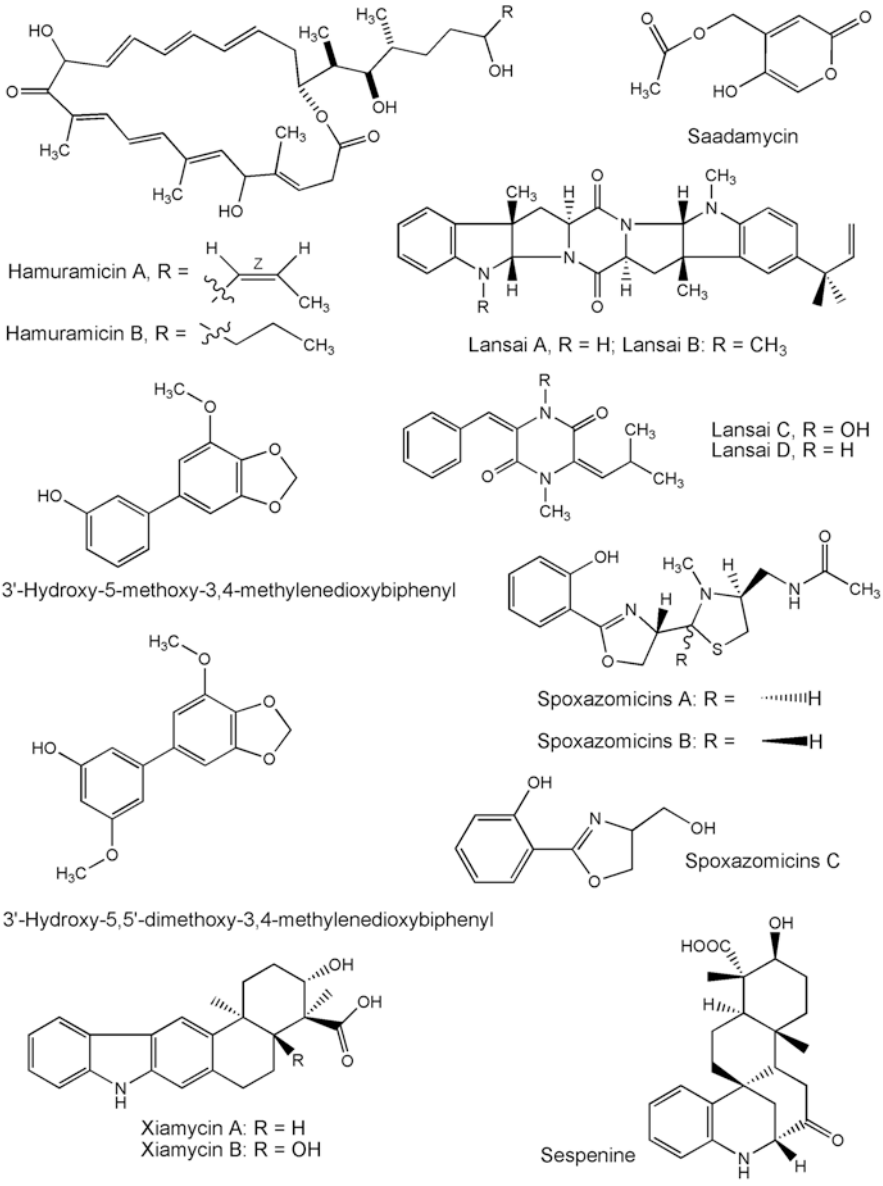

Fig. 8.3 (continued)

E- and P-selectin binding in vitro and thus prevented rolling of T cells. All the three macrolides Efomycin M, Efomycin G and Oxohygrolidin can inhibit the growth of both Gram-positive and Gram-negative bacteria and have antimalarial activity. Abierixin and 29-O-methylabierixin also displayed antimalarial activity (Supong et al. 2016).

8.7.9 Antimycin A18

Antimycin A18 was produced by an endophytic actinobacterium *Streptomyces albidoflavus* isolated from a leaf of a mangrove plant *Bruguiera gymnorrhiza* collected from Shankou, Guangxi Province, People's Republic of China. This compound was reported to have antifungal activities against plant pathogenic fungi (*Colletotrichum lindemuthianum*, *Botrytis cinerea*, *Alternaria solani* and *Magnaporthe grisea*) suggesting that it may use for protection of plants (Yan et al. 2010) (Fig. 8.3).

8.7.10 3′-Hydroxy-5-Methoxy-3,4-Methylenedioxybiphenyl

Streptomyces sp. BO-07 which was isolated from root tissue of the medicinal plant of Thailand *Boesenbergia rotunda* (L.) Mansf A was found to be the source of another two antimicrobial compounds, i.e., 3′-hydroxy-5-methoxy-3,4-methylenedioxybiphenyl and 3′-hydroxy-5,5′-dimethoxy-3,4-methylenedioxybiphenyl (Fig. 8.3). Both of these compounds have strong antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus* ATCC25932, *Bacillus cereus* ATCC7064, *Bacillus subtilis* ATCC6633) and moderate inhibitors against Gram-negative bacteria (*Escherichia coli* ATCC10536, *Pseudomonas aeruginosa* ATCC27853, *Salmonella Typhi* ATCC19430, *Serratia marcescens* ATCC8100) (Taechowisan et al. 2017).

8.7.11 Spoxazomicins

Spoxazomicins were included in novel antitrypanosomal alkaloids of the pyochelin family which were isolated from *Streptosporangium oxazolinicum* K07-0460, an endophyte from the roots of orchid. In vitro antitrypanosomal activities revealed that both Spoxazomicins A and B have strong antitrypanosomal activity against GUTat 3.1 strain of *Trypanosoma brucei brucei* with an IC_{50} value of 0.11 μg ml^{-1} and 0.55 μg ml^{-1}, respectively. However, Spoxazomicins C showed weak antitrypanosomal activity, with an IC_{50} value of 3.0 μg ml^{-1} (Inahashi et al. 2011) (Fig. 8.3).

8.7.12 Cedarmycins

Cedarmycins are novel butyrolactone antibiotics isolated from *Streptomyces* sp. TP-A0456, a plant-associated actinobacteria from stem of *Cryptomeria japonica.* Both of these compounds showed weak to moderate antibiotic activity against both Gram-positive and Gram-negative bacteria, while more potent activity against *Candida glabrata* having IC_{50} of 0.40 and 1.60 μgml^{-1}, respectively (Sasaki et al. 2001) (Fig. 8.3).

8.7.13 Fistupyrone

It is a microbial metabolite isolated from plant-associated *Streptomyces* sp. TP-A0569. Fistupyrone can inhibit the *in vivo* infection of the seedlings of Chinese cabbage caused by *Alternaria brassicicola* TP-F0423 (Igarashi et al. 2000) (Fig. 8.3).

8.7.14 Saadamycin

Saadamycin is another antibiotic isolated from endophytic actinomycetes *Streptomyces* sp. Hedaya48 which is active against dermatophytes and other clinical fungi (El-Gendy and El-Bondkly 2010) (Fig. 8.3).

8.7.15 Lansai A–D

These antibiotics were isolated from *Streptomyces* sp. SUC1, an endophytic actinobacterium from the aerial roots of *Ficus benjamina*. All the antibiotics showed weak activity against *Colletotrichum musae* with MIC>100 μgml^{-1} (Tuntiwachwuttikul et al. 2008) (Fig. 8.3).

8.7.16 Actinomycin D

It is a potent antibiotic from *Streptomyces* sp. Tc022, an endophyte from roots of *Alpinia galangal*. It showed bioactivity against plant pathogenic fungi *Colletotrichum musae* (MIC = 10 μg ml^{-1}) and *Candida albicans* (MIC = 20 μg ml^{-1}) (Taechowisan et al. 2006) (Fig. 8.3).

8.7.17 Clethramycin

Clethramycin is structurally similar to Linearmycin and was isolated from *Streptomyces hygroscopicus* TP-A0623, endophyte from the root of *Clethra barbinervis* collected in Toyama, Japan. It was reported to have strong bioactivity against yeast (*Candida albicans*, *C. glabrata*) and fungus (*Aspergillus fumigatus*), however weak activity against Gram-positive and negative bacteria (Furumai et al. 2003).

8.7.18 Hamuramicins

Two new compounds containing 22-membered macrolide-containing triene and trienone with an alkyl side chain, designated as Hamuramicins A and B (Fig. 8.3), were isolated from the cultured broth of an endophytic actinomycete *Allostreptomyces* sp. K12-0794. Both of these compounds showed growth inhibition activity against *Kocuria rhizophila* and *Xanthomonas oryzae* pv. *oryzae* (Suga et al. 2018).

8.8 Conclusion

Over the centuries medicinal plant species were used by humans for traditional benefits. Perusal of literature also disclosed that medicinal plant species are the treasure of novel bioactive molecules, among which some led to the discovery of new drugs. Endophytic bacterial population of medicinal plants which are relatively poorly investigated serve as an important component of biodiversity and as a promising source of antimicrobial compounds. Combinations of different cultivation-dependent and cultivation-independent techniques increase our understandings of analysing the diversity of bacterial endobiome and consequently understanding the mechanisms underlying the plant-endophyte interaction. An extensive characterization and identification of the diverse population also help to discover new antimicrobial compounds from them which lead to solve the present-day problems like the appearance of various life-threatening diseases and resistance to existing drugs which ultimately prove to be safe and efficacious for human healthcare.

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