Indo-Pak Medicinal Plants and Their Endophytes: An Emphasis on Nutraceutical and Bioactive Potential

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Abstract

The Indo-Pak region has deep historical roots of traditional medicine. In both Pakistan and India, the local population has relied upon the Unani-Tibb (Graeco-Arabic) and Ayurveda medicinal systems for centuries. With the increase in our understanding of ethnobotany and endophytes, the significance of the traditional plants in the region has also increased. The traditional Indo-Pak plants such as Neem and Tulsi have been studied not only for their wide array of pharmaceutical activities but also for their endophytes. Extracts of different parts of neem have been used as antimicrobial, antiviral, antimalarial, anti-carcinogenic, antipyretic, anti-ulcer and anti-inflammatory agents, whereas its seeds are a rich source of proteins and fatty acids. Latest researches have proved the nutraceutical potential of plants such as imli, amla and soanjna in the Indo-Pak region. Further understanding of these plants can lead to unbeatable bioactive and nutraceutical sources. In this chapter, we will focus on the traditional plants of the Indo-Pak region, their endophytes particularly the genus actinomycetes and the recent studies done on their diverse metabolites.

Keywords

Endophytes · Indo-Pak · Medicinal plants · Nutraceuticals
4.1 Introduction

Asia is the most populated continent of the world which boasts of more than 1.2 billion inhabitants (approx. 36% of the world population), and according to the United Nation’s (UN) definition, it comprises of 51 countries. The territories of this continent form a triangle, its one corner is Bosporus to the West, the second is Japan from the Northeast, and the third is Indonesia in the Southeast (Guilmoto and Oliveau 2018). The geographical boundaries of its south Asian region encompass seven countries, i.e. Pakistan, Bangladesh, Bhutan, Maldives, India, Nepal and Sri Lanka. Collectively, it is referred to as the South Asian subcontinent or South Asia, and if we consider the region, only including India and Pakistan, then it is known as the Indo-Pak subcontinent (Wangchuk et al. 2008; Shinwari and Qaiser 2011; Jain et al. 2018).

4.2 The Ethnobotany Prevailing in the Indo-Pak Subcontinent

Plants have been used as medicines as early as Neanderthal man with the earliest use reported in ancient Egypt in 1550 BC and in the code of Hammurabi in 1770 BC in Babylon. Other reports have come from the ancient cultures of China, Egypt, Africa as well as from the Indus valley civilization (Husain et al. 2008). A Sumerian clay tablet dating back 4000 years contained written remedies such as the use of mandrake and garlic for the relief of major disorders such as heart conditions (Mushtaq et al. 2018). Medicinal plant has been described as, ‘a plant containing substances in its organs that can be used for therapeutic purposes or as precursors for chemical pharmaceuticals’. The definition divides the medicinal plants into two categories, those that are used in crude formulations by local physicians and those that are used by the pharmaceutical industries (Husain et al. 2008). Some medicinal plants are important for their potential in research leading to new pharmacological drug development. Others are used widely as common remedies at home or are collected in bulk as raw materials for the pharmaceutical industries both synthetic and herbal (Walter et al. 2011).

Many of the commercial drugs have their basis in plant-derived medicine; one example is of morphine that was isolated in 1803 from *Papaver somniferum*. Its commercial form that is used as a painkiller was first introduced in 1870. Another painkiller aspirin was identified in the bark of *Salix purpurea* L. and first commercially introduced in 1899 (Mushtaq et al. 2018). Quinine is another well-known example; it was isolated from the bark of *Cinchona officinalis* L. Some other examples of drugs derived from ethnobotanical plants include vinblastine and vincristine from *Catharanthus roseus* L. and taxol from *Taxus baccata* L. Both medicines bearing immense potential against acute lymphoma and uterine carcinoma, respectively (Srivastava 2018).

The South Asian region contains an extraordinary diversity of 4600 communities that use around 2000 plants for their medicinal needs (Nakatsuka et al. 2017). Currently, about 84% of the people in India depend on these medicinal plants for
their routine health management through the traditional system of medicine implemented through the science of ethnobotany (Jain et al. 2018). The ethnobotanical science is described as the interaction between plants and people and the relationship that develops, leading to their use in healthcare. It is as old as the people themselves because evidence have proved that people living for centuries in one specific locality develop a rich understanding and knowledge about the local habitat and its resources. This information is passed on generation after generation through oral communication and practices. People of the Indo-Pak subcontinent have been healing themselves using medicinal plants for centuries (Jain et al. 2018).

The ethnobotanical system prevailing in Pakistanis is one of the oldest systems in the world. The country is unique because of its geography with areas such as Himalayans and Cholistan desert, both known for their floral diversity. The country boasts of more than 6000 species of higher plants out of which 12% are currently being used in various medicines (Jain et al. 2018; Tanvir et al. 2020). Of all the endemic plant species, 456 medicinal plants are used in local industries for 350 or more classical medical formulations. A number of studies have been conducted on the ethnomedicinal plants of Baluchistan, South Waziristan, Margalla Hills, motorway (M-2), Salt range (Kallar Kahar) and Nandiar Khuwarr catchment, Himalayan areas of the country to name a few. The local communities of the region are in a habit of using the natural resources of these plants for everyday ailments such as diarrhoea, cold, cough and fever. In addition, the reason of their more common use is that they are easily available, natural without side effects and are inexpensive. Since majority of the people belong to low-income families, they prefer to utilize the knowledge of the plants that have been passed down through generations; therefore, instead of expensive drugs they use herbal teas and powders (Ahmad and Husain 2008; Haq et al. 2011).

In India, evidence have been found of medicines based on plants in Ayurveda hymns as old as 1000 BC that described the use of over a thousand different medicinal plants for various ailments (Mushtaq et al. 2018). The first record of plant medicine was compiled in Rigveda that dates back to 4500–1600 BC. Much of the literature can be traced to Vedic records. When looking to the diversity of plants in India, much of the work has been done on investigating central India along with its northern and southern regions. Like Pakistan, India also possess a rich diversity of plants due to the variety of climate, altitudes and ecology. In central India, the areas of Chhattisgarh state and Madhya Pradesh possess the largest deciduous forests in the country (Jain et al. 2018). Himachal Pradesh is another state rich in medicinal plant flora (Srivastava 2018). The country itself is divided into 29 states and 7 territories, and so far 45,000 biodiverse plant species have been documented there (Rupani and Chavez 2018). The traditional healers that are estimated to be around 1.5 million in the Indian population use more than 7000 plants for their herbal formulations. If we talk about the manufacturing of such formulations, then the country has 7800 manufacturing units for their production (Pandey et al. 2013). The Indian herbal medicines often are blends of different plant species rather than a single species and some of the examples include Ubtan that is a blend of Santalum album, Cicer arietinum and Curcuma longa. Another example is of Parangichakkai...
chooranam consisting of *Euphorbia tirucalli, Indigofera aspalathoides, Euphorbia antiquorum, Enicostemma littorale, Azima tetracantha* and *Smilax china*. The blends such as these are often given to elderly and young children as tonics and used daily by the members of the family. Herbal formulations such as these account for around 25,000 in number (Rupani and Chavez 2018; Pandey et al. 2013).

### 4.3 Traditional Systems of Medicine Prevailing in the Indo-Pak Region

Traditional medicine refers to the knowledge of the medicine acquired through the practice based on theories, experiences and local beliefs that are indigenous to a specific culture for the treatment of a particular illness. This traditional medicine when followed by other cultures is referred to as alternative medicine (Srivastava 2018). In the Indo-Pak region and the surrounding countries such as Bangladesh, Nepal and Sri Lanka, there are several healing traditional systems that are in practice alongside or in place of allopathy for centuries (Rupani and Chavez 2018).

#### 4.3.1 Tibb e Unani

Traditional Unani medicine is a part of the Pakistani culture and is practised by the traditional physicians (Hakims) belonging to various herbal centres (Tibbi Dawakhana). The word ‘Unani’ means ‘Greek’ in the Urdu language (the prevailing language in Pakistan). The origin of this medicinal system was from Hippocrates, the well-known Greek philosopher (460–377) and his colleagues; therefore, it is referred to as ‘Tibb e Unani’. It was well established under the Arab and Persian empires and thrived, and was later brought to the subcontinent in the mid of the fourteenth century through the Muslim scholars. Various methods adopted by Tibb e Unani are regimental therapy, diet therapy and pharmacotherapy and are heavily dependent on medicinal plants (Husain et al. 2008; Parveen et al. 2019). The philosophy of this system of medicine is based on the principle of four elements, earth, air, fire and water. Each element has a different temperament (hot, cold, dry and wet) and that the body is made up of these four elements. A balance of four body fluids, blood and phlegm, black and yellow bile, is required to maintain health. The normalization of the body is examined through the body wastes, and any required treatment is carried out through diet, herbs, exercise and massage therapy (Rupani and Chavez 2018). There are 300–350 Tibb-e-Unani manufacturing companies in Pakistan. The country is also one of the main exporters of medicinal plants due to its massive Pansara (crude drug) market system (Hussain et al. 2009; Tanvir et al. 2020). Unani medicinal practice is also prevalent all over India (Sundarrajan and Arumugam 2017).
4.3.2 Ayurveda

Ayurveda is an ancient Indian system of medicine that has been in practice for thousands of years. Historical reports suggest it has been in practice since 1500 BC (Prasher et al. 2016). Ayurveda is a Sanskrit word that can be divided into Ayu meaning life and veda meaning knowledge; therefore, the complete term means ‘life knowledge’ or ‘knowledge of life’ (Sen and Chakraborty 2017). Its therapies are based on various herbal concoctions, metals and minerals. Like the Tibb e Unani, the principle of Ayurveda is based on three main elemental substances or energies that are called doshas, i.e. air, fire and water. Their balance is essential for the maintenance of health (Rupani and Chavez 2018). This form of treatment takes into consideration the body, the mind and the spirit (Mukherjee et al. 2008). The classical texts of Ayurveda were written focusing on internal medicine (Charaka Samhita) and on surgery (Susruta Samhita). Further on, subdivisions were added which included gynaecology, obstetrics and paediatrics (Kaumar-abhrtya), toxicology (Agada Tantra), psychiatry (Bhutavidya), aphrodisiology (Vajikarana) and supra-clavicular diseases (Salakya) (Sen and Chakraborty 2017). Another one of the major subdivisions of its pharmacology is ‘Medhya rasayana’, which is the enhancement of memory and intellect using medicinal plants (Mukherjee et al. 2008). Currently, considerable analysis is been conducted on pharmacology, chemistry and clinical treatment of Ayurvedic medicines. Several pharmaceutical giants have changed their procedures and methods to include medication from natural products (Patwardhan et al. 2004). The people of the northern part of India and Kerala are the ones that mainly practice Ayurveda medicinal system (Sundarrajan and Arumugam 2017).

4.3.3 Siddha

Siddha medicinal system comes from the Tamil community in the southern part of India and is believed to be a symbol of their culture. It is reported to be derived from Dravidian culture and grew during the time of the Indus Valley Civilization. It is heavily inspired by Taoism and Chinese alchemy. Originally believed to resemble the Ayurveda health system in many aspects, it is said to have been developed by 18 Tamil sages called ‘Siddhars’ (Sen and Chakraborty 2017). The fundamental idea in this system is that a healthy body will reach a healthy soul. Diet, meditation, yoga and exercises are the premise of physical and mental recovery. The aim is to balance the three doshas (Rupani and Chavez 2018). The system is divided into three main divisions on the basis of use, either it depends on the treatment with plants (Moola vargam), animals (Jeeva vargam) or minerals (Thaathu vargam). Whatever division is used, a trained Siddha practitioner is only allowed to use it under the law of the Government of India. Many of the formulations are passed down to generations orally and are not documented and mainly confined to the communities in the southern part of the country (Sundarrajan and Arumugam 2017).
4.4 Indo-Pak Medicinal Plants

No matter what traditional medicinal system is used, plants remain the main source of their treatment strategy (Sen and Chakraborty 2017). Plants are capable of defending themselves through the mechanism that produces secondary metabolites known as natural products. Such products have been used for thousands of years to improve human health and still continue to give array of therapeutic activities based on the origin, habitat and specific activity possessed by the plant (Bernardini et al. 2018). Recently, more and more people prefer plant-based medicines for their medical needs. The reason being that natural products are safer than synthetic medicines that come with some serious side effects and microbial resistance. Therefore, the natural products are considered a healthy life style, and their constituents have favourable long-term effects on staying healthy. According to estimates, 75% of plant-based drugs worldwide are discovered through traditional medicines. Only in India, about 70% of the manufactured anticancer and cardiovascular drugs have their basis from medicinal plants (Sen and Chakraborty 2017; Srivastava 2018). Medicinal plants are crucial to the livelihoods of poor communities all over the world (Joshi and Joshi 2001; Shinwari and Qaiser 2011).

4.4.1 Azadirachta indica

*Azadirachta indica* (Neem) in Latin translates to ‘free tree of India’ (Rupani and Chavez 2018). It originated in India and Burma and is also referred to as ‘a tree for solving global problems’ and the ‘rural pharmacy’ (Chen et al. 2018). The reason it being named so is because all the parts of *A. indica* are used in herbal medicines. The plant is known for its active metabolite azadirachtin that has been reported to inhibit retinoic acid-mediated responses and TNF-α activity (Rupani and Chavez 2018). As many as 200 limonoid compounds have been isolated from different parts of *A. indica*, and azadirachtin remains the major compound. Other secondary metabolites include nimbin, salanin, epoxy/hydroxy-azadiradione and azadiradione (Gowda et al. 2019). The plant also possesses bioactive triterpenoids, volatile oils, nimbidin, nimbinitin, nimbin, salannin, β-sitosterol 6-desacetylnimbin and meliantriol (Rahal et al. 2019). The active metabolites nimbidin and gedunin have been found to possess potent antifungal activity (Asif 2012; Al-Samarrai et al. 2012). Other metabolites such as nimbolide displayed radical scavenging activity and was observed to inhibit the event of DMBA (7,12-dimethylbenz(a)anthracene)-induced carcinoma. Its presence resulted in upregulation of inhibitors and detoxification enzymes (Priyadarsini et al. 2009).

4.4.2 Ocimum sanctum

*Ocimum sanctum* (Linn.) is from the family Lamiaceae and is referred to as ‘Holy Basil’ in English and ‘Tulsi’ in Urdu, Hindi and Sanskrit (Joshi et al. 2018). It grows
in the subtropical and tropical regions of the world. The plant is associated with a novel fragrance, and all aerial parts of the plant have been reported for a wide range of biological and pharmacologic activities (Surkar et al. 1994), particularly its leaves and seeds are used in Ayurveda medicines (Shah and Patil 2019). *O. sanctum* has been studied for its significant antiviral potential against the new castle disease virus (NDV), vaccinia virus (VACV) and infectious bursal disease virus (IBD). *O. sanctum* leaf extracts increased the survival rate in patients infected with hepatitis virus and suffering from viral encephalitis (Prakash and Gupta 2005; Goothy et al. 2020). A study proved that consumption of *O. sanctum* for 3 days gives relief in respiratory diseases like asthma. It is also effective against pain, diarrhoea, dry cough and fever that are common symptoms of SARS-COV-2. Existing literature supports the use of *O. sanctum* against SARS-COV-2; however, lack of standard formulation limits its use (Goothy et al. 2020).

Recent reports highlight the nutraceutical potential of some bioactive compounds like Eugenolin *O. sanctum* (Ghosh et al. 2013; Dureja et al. 2003). Figure 4.1 shows young plants of *Azadirachta indica* (Neem) and *Ocimum sanctum* (Tulsi) growing in the nursery of University of Veterinary and Animal Sciences (UVAS), Lahore, Pakistan.

### 4.5 Nutraceutical Potential

Stephen DeFelice first coined the term ‘nutraceuticals’ in 1989 to describe the molecules that can be used singly or in combination as a supplement in the diet for in-born or age-related deficiencies. In 1996, the definition was further elaborated and described it as any food component that is nontoxic and proven for its health benefits. Nutraceuticals are sold as product which have been isolated and purified from food and are used to provide protection against chronic diseases (Shinde et al. 2014; Asif and Mohd 2019).

In the Indo-Pak region, a large segment of the population belongs to the lower class and lower middle class which lack the sufficient capacity to purchase the food to maintain a balanced diet. In India, the urban and rural population approximately 30% and 34%, respectively, consume more dietary fat than the recommended levels resulting in a risk of cardiovascular disorders and diabetes. The WHO report states
that the largest number of patients with diabetes and cardiovascular diseases reside in India (Pandey et al. 2013). In Pakistan, according to the national diabetes survey, the occurrence of diabetes is as much as 26.3% (27.4 million people), and 47 million people are hypertensive in a population of 207.77 million (Basit et al. 2019). Recently, another major health problem of liver disorder is also spreading rapidly in the Indo-Pak society. Therefore, only a diet rich in antioxidants can limit oxidative damage and related disorders (Ahmed et al. 2020). Nutraceuticals and natural antioxidants can be used as a therapeutic tool against diseases such as diabetes, blood pressure, cholesterol, arthritis, pain, cough, cold, cancers, digestive disorders as well as depression (Asif and Mohd 2019).

A large number of medicinal plants have been in use for centuries that possess macro- and micronutrients such as bioactive peptides, polyunsaturated fatty acid, carbohydrates, plant polyphenols, proteins, vitamins, minerals, oligosaccharides and carotenoids for maintaining a normal metabolism and enhancing health (Asif and Mohd 2019).

4.5.1 **Tamarindus indica** (Linn.)

*Tamarindus indica* (Fabaceae) is the Latin binomials for ‘Tamarind’ and is also known as ‘Imli’ in Urdu and Hindi. It has been widely used in traditional medicinal systems for centuries. The fruit pods are edible and are rich source of β-carotene, malic and ascorbic acid. The leaves, immature pods and the flowers contain a significant amount of vitamins such as riboflavin, thiamine, and niacin besides the fibre, proteins and fats. The fruits, especially its pulp, is rich in essential phytochemicals, vitamin A, C, calcium and phosphorus as well as tartaric acid. *T. indica* seeds are a vital source of proteins, potassium, magnesium, calcium and phosphorus. The seed coat is rich in tannins and fibres. The proteins of the seeds have a high amount of cysteine and methionine amino acids and can be added to protein poor foods as supplement and serve as its cheap source to overcome protein malnutrition. They also contain a high amount of polysaccharides. Overall, *T. indica* is an excellent herb used in the prevention of various forms of cancers, to boost immunity and to lower blood cholesterol (Bagul et al. 2015; Abdallah and Muhammad 2018; Soni and Singh 2019).

4.5.2 **Emblica officinalis** (Gattertn)

*Emblica officinalis* (Euphorbiaceae), commonly known as Amla, is a medicinally important plant of the Indo-Pak subcontinent and is native to its tropical and subtropical region. It is commonly referred to as Indian gooseberry, and the fruits (Pale green berries) occupy a major place in traditional medicinal systems of this region (Hasan et al. 2016; Fazil and Nikhat 2019; Priya and Islam 2019; Fazil and Akram 2019). The fruit of *E. officinalis* is rich in vitamin C as compared to other fruits such as pomegranate, lime and grapes. The nutritional constituents of its fruit
are such that it possesses a large amount of carbohydrates, fibre and protein. It is rich in iron and minerals such as calcium, potassium, magnesium, zinc, phosphorous, copper, chromium and nicotinic acid (Fazil and Nikhat 2019; Variya et al. 2016; Abdulhamza 2013).

### 4.5.3 *Moringa oleifera* (Lam.)

*Moringa oleifera* (Moringaceae) commonly known as drumstick tree is a fast-growing draught-resistant tree (Ashok Kumar and Pari 2003). Due to its ability to resist drought, the plant has the ability to adapt well in the dry and hot regions of the Indo-Pak subcontinent (Pandey et al. 2011). It is reported to originate in the Indian Himalayan region including Pakistan, Afghanistan and Bangladesh (Godinez-Oviedo et al. 2016; Singh et al. 2019). In regional language, it is known as Soanjna, Shajna or Sainjna (Pandey et al. 2011). Figure 4.2 shows young plants of *Tamarindus indica*, *Emblica officinalis* and *Moringa oleifera* growing in Lahore, Pakistan.

*M. oleifera* has been reported to contain over hundred important nutrients including proteins (albumin, gluten, globulin and prolamin) and dietary fibres. The seeds have high lipid content that include stearic acid, palmitic acid, oleic acid, behenic and arachidic fatty acids. Other nutrients include vitamins (vitamins A and C), minerals (phosphorus, calcium, potassium and iron), essential amino acid methionine, beta-carotene and omega-6 and -3 fatty acids (Singh et al. 2019; Pandey et al. 2011; Godinez-Oviedo et al. 2016). The leaves of *M. oleifera* contain vitamin C seven times more than oranges, beta-carotene more than carrots, double the protein and four times more calcium than in milk. The amount of potassium is three times higher as compared to bananas (Asare et al. 2012). *M. oleifera* is reported to contain novel phytoconstituents made up of unusual sugar rhamnose and it found to be

![Fig. 4.2](image-url) Young trees of (a) *Tamarindus indica* (Imli), (b) *Emblica officinalis* (Amla) and (c) *Moringa oleifera* (Soanjna)
The plant is also rich in antioxidants, terpenoids, flavonoids, tannins, saponins, alkaloids, phenols, and glycosides. Table 4.1 summarizes the major medicinal applications of the shortlisted plants of the Indo-Pak region.

### 4.6 Endophytes

Endophytes are the organisms that are found growing inter or intracellularly, locally or systemically within the internal tissues of plants (stem, roots, leaves and seeds) without causing visible infection or disease symptoms. In endophytism, the infections by the endophytes are unassuming and transiently symptomless; therefore, it is suggestive that every plant harbours such endophytes. Their diversity, however, may depend on factors such as the plant species, nutrient availability, environmental conditions and interactions with other microbes in the soil. Studies suggested that endophytes often reside within the particular host for a part of their life cycle (De Silva et al. 2019; Eid et al. 2019). Endophytes display various degrees of host specificity in plants colonization pattern; they also exhibit different life styles ranging from facultative to obligate and can propagate through vertical and horizontal transmission (Caradus and Johnson 2019). How these endophytes originated are not fully understood; however, two hypotheses are put forth on their origin inside the plants. One hypothesis regards them as originating from the host plant’s chloroplast and mitochondria; therefore, it has similar genetic background as the host. This theory is regarded as the endogenous hypothesis, whereas, the exogenous hypothesis is based on the assumption that these endophytes were introduced to the plant from the soil through any wound on the roots or through the nutrient and water channels (Eid et al. 2019). These endophytes play important role in the growth of their host plant either by secondary metabolites production or by assimilation of nutrients. Many microbes have been found to be associated to a plant host; these microbes include bacteria, fungi and actinomycetes. Studies suggest that the communities of these bacteria mainly colonize the host plant roots. Among all the bacterial communities, actinomycetes are considered the second most abundant organisms (>30%) in the soil. They travel from the soil into the plant through the lateral root junction, spaces between the root hairs and the epidermal cells of the seeds (Eid et al. 2019).

Endophytes are known to protect their host plant from various abiotic and biotic stresses through the production of phytohormones and bioactive secondary metabolites. Hundreds of natural products have been reported in various studies that include alkaloids, terpenoids, flavonoids, steroids, benzopyranones, tetralones, quinones, phenolic acids, saponins, xanthones, tannins and many others (Ebrahim et al. 2019). Most of these natural products are bioactive compounds with various functions like antibacterial, anticancer and biological control agents (Joseph and Priya 2011).
| Sr. no. | Plant   | Common name | Family       | Medicinal application(s)                                                                 | Reference(s)                                                                                                                                 |
|--------|---------|-------------|--------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| 1.     | *Azadirachta indica* | Neem | Meliaceae | Against eczema, scabies, psoriasis, antimalarial agent, spermicidal, anti-inflammatory and immunological, anti-mutagenic, antiviral, antimicrobial, antioxidant and anti-carcinogenic | Rupani and Chavez (2018), Gowda et al. (2019), Maity et al. (2009), Jones et al. (1994), Sharma and Saksea (1959), Subapriya and Nagini (2005), Androutsopoulos et al. (2009), Rahal et al. (2019) |
| 2.     | *Ocimum sanctum* (Linn.) | Tulsi | Lamiaceae | Anticancer, antimicrobial, antifungal, hepatoprotective, analgesic and antiulcer agent, against asthma, malaria, diarrhoea, dysentery, skin diseases | Sivareddy et al. (2019), Mohan et al. (2011), Prakash and Gupta (2005)                                                                 |
| 3.     | *Tamarindus indica* | Imli | Fabaceae | Used for arthritis, heart diseases, blood pressure, indigestion, diarrhoea, cancer, immunity, throat infections and diabetes | Bagul et al. (2015)                                                                                                                                 |
| 4.     | *Emblica officinalis* | Amla | Euphorbiaceae | Used for the disorders of the hair, skin, disorders of gastro-intestinal central nervous system | Fazil and Nikhat (2019), Priya and Islam (2019), Fazil and Akram (2019), Hasan et al. (2016)                                                                                 |
| 5.     | *Moringa oleifera* Lam. | Soanjna | Moringaceae | Antitumor, antihepatotoxic, antiurolithiatic, analgesic agent, used to treat hypertension, regulate thyroid hormone’s functions | Asare et al. (2012), Ashok Kumar and Pari (2003)                                                                                             |
4.6.1 Endophytic Actinomycetes

Actinomycetes are aerobic, Gram-positive, filamentous bacteria having a higher GC content in their DNA. They resemble fungi in morphology and form branching filaments and produce asexual spores (Masand et al. 2015; Das et al. 2018; Tandale et al. 2018). Due to their diverse metabolic potential, they have become the dominant producers in the biotechnology industry for natural bioactive metabolites. These metabolites include and are not limited to antibiotics, phytohormones, immunomodulators and enzymes. Because of this reason, the actinomycetes contribute towards the development of 90% of the commercially available antibiotics (Das et al. 2018). Plants are considered host to many endophytic actinomycetes. Recently, several studies have been done for their isolation from the rhizosphere as well as from the roots of many plants such as tomato, wheat, banana and maize (Akshatha et al. 2016). Considering the isolation of actinomycetes in the rhizosphere as well as from the plant roots, it may give us a clue regarding the exogenous hypothesis of endophytes colonization. In addition, they might have been introduced to the plants in their early growth or through the damage to the roots.

Many secondary metabolites produced by the endophytic actinomycetes are not only useful for the plant itself but also have commercial and medicinal importance (Kumar and Jadeja 2016). They have also been observed to be useful in the agriculture industry through the production of phytohormones. These endophytic actinomycetes have also been reported to produce novel antifungal agents such as cedarmycins A and B and the broad-spectrum antibiotics munumbicins E-4 and E-5. Many endophytic actinomycetes have been reported being bioactive against a variety of soil-borne fungal plant pathogens including the major pathogens, *Fusarium oxysporum* and *Rhizoctonia solani* (Chandrakar and Gupta 2018). The endophytic actinomycetes related to tropical plants are not fully studied. However, in recent years endophytic actinomycetes and their metabolites have become a hot topic considering the effective production of new compounds leading to development of new drug agents (Kumar and Jadeja 2016). There is a need to explore the ethnopharmacologically important plants for such endophytic actinomycetes that may provide a cure for acute and chronic illness (Chandrakar and Gupta 2018).

4.6.2 Association of Endophytic Actinomycetes with Their Host Plant

Medicinal plants of the Indo-Pak region have a strong ethnobotanical history that makes them favourable for isolating endophytic actinomycetes. In the last decade, a significant amount of work has been carried out on isolation and characterization of endophytic actinomycetes particularly related to the medicinal plants of the Indo-Pak region. Verma et al. (2009) described 55 different actinomycetes from *A. indica*, and majority of them were recovered from the roots (54.4%) and lesser from other parts such as the stem (23.6%) and the leaves (21.8%). The prevalent genus among them was *Streptomyces* that made up of the 49.09% of the total isolates. Among the
55 isolates, majority of them showed antimicrobial activity (antibacterial and antifungal activity). Nawaz et al. (2018) isolated 28 endophytic actinomycetes from various parts of both A. indica and O. sanctum with prominent activity against veterinary and human pathogens that included Campylobacter jejuni, Proteus mirabilis, Salmonella enteritidis and Acinetobacter baumannii. Another study by Gohain et al. (2015) also on A. indica described the majority of the endophytic actinomycetes isolates to be those of Streptomyces sp. and a small number from other genus such as Micromonospora. In the case of study by Kuncharoen et al. (2019), a novel strain was isolated from A. indica A. Juss. var. siamensis Valeton roots. Another rare strain of endophytic actinomycetes, Rhodococcus qingshengii, was isolated from the roots of A. indica by Saini et al. (2016). The strain produced anti-diabetic phenolic compounds that were observed to inhibit α-glucosidase and α-amylase resulting in delayed glucose absorption. In this context, Akshatha et al. (2014) worked on endophytes of two well-documented anti-diabetic plants Rauwolfia densiflora (Apocynaceae) and Leucas ciliata (Lamiaceae). Interestingly, two endophytic actinomycetes strains, Streptomyces longisporoflavus and Streptomyces sp., also displayed anti-diabetic activity. It is now a proven fact that the endophytes residing within the medicinal plants mimic chemistry of their host; the isolation of such endophytic actinomycetes is another proof of this fact. This approach provides a cheaper source of α-glucosidase and α-amylase that are the commercially available inhibitor used for diabetes. India and Pakistan, both being the countries with higher prevalence of diabetes, can use such endophytic actinomycetes to curb this chronic progressive disease.

Besides medically important compounds, endophytic actinomycetes in A. indica were also reported to produce compounds such as anti-insecticidal agents as described by Chen et al. (2018). An endophytic Streptomyces albidoflavus was found to produce compounds that showed 83% mortality in aphids. Since it is already reported that the active compound azadirachtin from A. indica is a potent insecticidal agent; therefore, it can be hypothesized that endophytic actinomycetes residing inside it may be producing azadirachtin.

Gangwar et al. (2014) studied the endophytic actinomycetes residing within the tissues of Ocimum sanctum. As with the reports from A. indica, majority of the isolates were obtained from the roots, and they were found to be belonging to the genus Streptomyces. However, another study by Singh and Padmavathy (2015) on the endophytic actinomycetes population of O. sanctum resulted in the isolation of rare actinomycetes species, Nocardiopsis dassonvillei and Nocardiopsis synnemataformans.

There are many endophytic actinomycetes reported from Emblica officinalis because of it being an important ethnomedical plant of the Indo-Pak region. A recent study by Gohain et al. (2019) explored the diversity of the endophytic actinomycetes harboured by the plant. The study observed the majority of the isolates belonged to the genus Streptomyces that is in agreement with the studies conducted earlier. However, other genus such as Microbispora sp. and Micrococcus sp. were also reported shedding a light on the diversity of the endophytes harboured by this medicinal plant. Another study on the endophytic actinomycetes of E. officinalis...
by Gangwar et al. (2015) reported the presence of Microbispora and Micromonospora genus as well along with the genus Streptomyces. Their isolates were observed to be prolific producers of siderophores, indole acetic acid and were also observed to solubilize phosphates. Other endophytic actinomycetes reported by studies such as Singh and Padmavathy (2014) were observed to be producing extracellular enzymes, amylases, lipases and cellulosics. Apart from actinomycetes, some fungal endophytes have also been reported from E. officinalis. A study by Nath et al. (2012) described the isolation of Phomopsis sp. and Xylaria sp. that were observed to be bioactive against pathogens such as Salmonella enterica ser. Paratyphi, Enterococcus faecalis, Streptococcus pyogenes and Candida albicans. Another endophytic fungal strain Nigrospora oryzae was isolated from the leaves of E. officinalis by Rathod et al. (2014). The strain was observed to be producing an antifungal compound, griseofulvin. Prior studies have reported the production of this bioactive compound from Penicillium.

As compared to E. officinalis, in the case of Tamarindus indica and Moringa olifera, recent studies have not reported the isolation of endophytic actinomycetes. Although studies have been carried out to find out other endophytes harboured by these important medicinal plants, the study by Chigurupati et al. (2020) shares interesting information regarding the endophyte population residing within the T. indica leaves. The authors report the isolation of a strain Bacillus velezensis that was observed to be bioactive particularly against major nosocomial pathogens, P. aeruginosa and N. gonorrhoeae. Dalee et al. (2015) reported a high count of endophytic fungal strains from T. indica stems, and the extracts of these strains gave prominent activity against major pathogens such as Salmonella typhi. However, interestingly, an earlier study by Radu and Kqueen (2002) reported the isolation of endophytic fungal isolates from T. indica that did not display any activity against pathogens such as Salmonella typhimurium. And, another earlier study by Taechowisan et al. (2003) reported no endophyte isolates from this plant. In case of M. olifera, recent studies by Kaur et al. (2020), Arora and Kaur (2019) have described the isolation of Aspergillus fumigatus, an endophytic fungus that possessed antimicrobial potential against prominent pathogens including methicillin-resistant Staphylococcus aureus (MRSA). Another recent study by Atri et al. (2020) reported the isolation of other fungal species such as Fusarium sp., Colletotrichum sp., Cladosporium sp. and Alternaria sp. The study by Mosquera et al. (2020) also describes the isolation of fungal species, Cladosporium sp. and Penicillium sp. from M. olifera.

Other studies such as by Akshatha et al. (2016) focused on the ethnomedicinal plants such as Cajanus lineatus (Maesen), Leucas ciliata, Rauwolfia densiflora and Gomphostemma heyneanum. The isolation of 135 endophytic actinomycetes from them gave an idea that these plants are a rich source for the isolation of rare Streptomyces sp. such as Streptomyces globosus, Streptomyces sedi, Streptomyces hypolithicus, Streptomyces longisporoflavus, and Streptomyces phaeochromogene. The bioactive compounds identified from these isolates included phenol derivatives; fatty acids such as palmitic acid and octadecanoic acid, esters such as butyl ester, diisobutyl ester, and phthalic acid were identified. Interestingly all these compounds
were observed to be strong antioxidants. Another endophytic *Streptomyces* strain, *Streptomyces parvulus*, was reported to produce potent antimicrobial compounds. The strain was isolated from the roots of *Aloe vera* Brum and gave prominent bioactivity against multidrug-resistant *Klebsiella Pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Proteus vulgaris*, *Aspergillus niger* and *Candida albicans*. On further analysis, the polypeptide nature of the produced antimicrobial was ascertained. The strains were observed to be quite versatile as they also produced the antitumor compounds, actinomycin D and actinomycin X (Chandrakar and Gupta 2018). Some of the *A. indica* and *O. sanctum* endophytic actinomycetes recognized as producers of antibacterial agents are shown in Fig. 4.3.

### 4.7 Conclusion

The focus of this chapter was to explore the rich history of ethnobotany prevailing in the Indo-Pak region, the reason behind the use of their indigenous plants for medicinal and nutritional purposes as well as the endophytes residing in them. The regions of India and Pakistan have centuries old medicinal systems relying on the indigenous medicinal plants. Such plants have been the focus of the studies for endophytes, especially the endophytic actinomycetes population residing in them. The presence of such endophytes in them may be the reason behind their use for the treatment of a variety of illness for centuries. Also in such a unique plant environment, the actinomycetes may acquire the ability to produce novel compounds. Even though a lot of research has focused on the plants of this region, yet a large number of plants still remain unexplored. Even with the rising level of interest for the search
of novel endophytes producing new compounds each year, it is safe to say that we have just touched the tip of the iceberg.

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