Biotechnology Reports 30 (2021) e00629

Contents lists available at ScienceDirect

Biotechnology Reports

journal homepage: www.elsevier.com/locate/btre

Review

Bioprospecting of endophytes in medicinal plants of Thar Desert: An attractive resource for biopharmaceuticals

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ARTICLE INFO

Article history:
Received 20 October 2020
Received in revised form 28 April 2021
Accepted 9 May 2021

Keywords:
Endophytes
Medicinal plants
Bioactive molecules
Vegetation
Endomicrobial diversity
Biopotential

ABSTRACT

Endophytes live asymptomatically within the healthy tissues of plant parts of the host, has grabbed the attention of ecologists, chemists, and researchers to have a broad spectral of biotechnological potential. It has been proven that almost all plants harbor endophytes within themselves. Numerous studies indicated that endophytes act as chemical synthesizers of the secondary metabolites of their host plant. Various medicinal plants of the Thar Desert have been used by the local folks of the Rajasthan to treat several diseases ailments for time immemorial. On the basis of their prior knowledge of ethno-pharmacological usage of medicinally important plants of Thar Desert, several researchers directed their studies in search of endophytic microflora of such medicinally important plants for the discovery of novel bioactive molecules of pharmaceutical importance, for instance, taxol producing endophytic fungus *Phoma* sp. isolated from *Calotropis gigantea* as well as *Aspergillus fumigatus*, an endophytic fungus reported from *Moringa oleifera* demonstrated an effective antibiofilm, antimicrobial and antiproliferative activity. This review sheds light on the endophytic microflora of the ethnomedicinal plants of the Thar Desert and their biopotential as a promising source of pharmaceutically important naturally derived compounds.

1. Introduction

The Great Indian Desert or The Thar Desert is spread over about 0.32 million km^2 area of the earth's surface which is approx. about 10% of the total geographic region of India [1]. Despite being one of the world's smallest deserts, it harbors a wide range of habitats, and biodiversity [1]. The arid climatic condition of the Thar Desert is characterized by low humidity, sandstorm, less precipitation, and extremes of diurnal and annual temperature. A wide range of flora, such as bryophytes, pteridophytes, lone gymnosperms (*Ephedra foliata* Boiss. ex C.A. Mey), and angiosperms adapted themselves to this harsh environmental condition which is generally categorized as hydrophytes, xerophytes, and halophytes according to their peculiar form. Plenty of medicinal plants are found in the desert [2]. Medicinal plants play a crucial role to cure various human diseases as they are sources of various bioactive molecules. These medicinal properties of plants are attributed to bioactive molecules, comprising simple alkaloids, anthraquinones (physcion, emodin, and chrysophanol), naphthopyrone glucosides, phenolics, rotenoids, saponins, steroids (β-sitosterol, carpesterol, and ecdysterone), and terpenes [2]. These bioactive molecules are either synthesized by plants or by some microbial consortium residing inside the plant parts asymptomatically. This microbial community resides in the plants is known as endophytes. The term endophyte was coined by De Barry in 1866. The distribution of endophytic microorganisms varies with the host range however mostly these plant-associated microbes have been isolated not only from aboveground plant parts but also from belowground plant parts too [3,4]. In addition to this, several studies have also depicted that endophytes help plants to mitigate biotic and abiotic stress [5]. The literature suggested that these endophytes may also be the reason behind the plant is being used to cure some diseases, in the light of the discovery of the production of billion-dollar anticancer drug paclitaxel by endophytic fungus *Taxomyces andreanae* residing inside the taxol producing plant *Taxus brevifolia* Nutt. This discovery proved itself as a novel source of paclitaxel without destroying the *Taxus* plant. This discovery proves to be the most eminent example of metabolite production by the endophytic microbiome [6,7].

Abbriviations: ISM, Indian summer monsoon; DDW, Double distilled water; PDA, Potato dextrose agar; SCA, Starch casein agar; ITS, Internal transcribed spacer; CF, Colonization frequency; MIC, Minimum inhibitory concentration; EtOAc, Ethyl acetate.

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https://doi.org/10.1016/j.btre.2021.e00629

These naturally derived secondary metabolites from medicinal plants and their complex endomicrobiom lives within plant parts have strong analgesic, antiarthiritic, antimicrobial, anticancer, antioxidant, anti-inflammatory, antiparasitic, hepatoprotective, hypolipidemic, insecticidal, and anticancerous activities [3]. Around three dozen out of 700 plant species of the desert area are known to have medicinal properties. Some of these are *Solanum nigrum* L., *Solanum surattense* Burm. f., *Phyllanthus niruri* L., *Mucuna pruriens* (L.) DC., *Justicia adhatoda* L., *Ocimum sanctum* L., *Ricinus communis* L., *Calotropis procera* (Aiton) W.T.Aiton, *Calotropis gigantea* (L.) W.T. Aiton, *Ziziphus mauritiana* Lam., *Withania somnifera* (L.) Dunal, *Moringa oleifera* Lam., *Salvadora oleoides* Decne., *Salvadora persica* L., *Prosopis juliflora* (Sw.) DC, *Euphorbia hirta* L., *Aloe vera* (L.) Burm.f., *Acacia nilotica* (L.) Delile, *Chenopodium album* L., *E. foliata*, *Tribulus terrestris* L., *Datura metel* L., *Datura stramonium* L., etc. [2]. The exploration of such bioactive molecules producing endophytes of medicinal plants may provide a basis for lead compounds for the development of novel drugs. The major advantage of using endophytes in drug production is that one can obtain a compound of plant origin without causing much harm to the plant community. Various biologically active compounds such as taxol, vincristine, camptothecin, piperin, azadirachtin, etc. have been isolated from endophytes. Nowadays, the production of a number of novel and naturally derived bioactive molecules is attributed to endophytic microbes of medicinally important plants. These bioactive molecules are exploited in the field of agriculture, medicine, and industry [8]. So, the ethnopharmacologically important plants with useful ethnobotanical history are likely to be an appropriate candidate for the study of endomicrobiome, since the medicinal property of that plant may be attributed to more to its endomicrobiome than the plant itself [9,10]. Considering this rationale and also the fact that since the flora of the Great Indian Thar Desert is full of ethnopharmacologically important plants have been studied so far for their endophytic community and biopotential, therefore, this review encompasses the recent progress being done in the exploration of such plant resident microbes.

2. Ecology and vegetation of Thar Desert

The Great Indian State Desert or The Thar Desert lies between the Indus River in Pakistan and the foothills of Aravalli ranges running diagonally across the Rajasthan state. However, it stretches at the eastern end of the extensive arid realm along the Tropic of Cancer that comprising the hyper-arid Sahara, the Rub-al Khali, and the Lut. Nevertheless, the Thar desert has less arid climatic condition than those of extreme deserts due to its position between two major rain-carrying climate systems, the Indian summer monsoon (ISM) and a Mediterranean westerly system that brings showers about 100–500 mm during the rainy season and occasionally of <100 mm during the winter and the spring, respectively [11]. The state of Rajasthan stretches between 23°04–30°11 N and 69°29–78°17 E, covering around 342,239 km^2 areas on the land that is about 10.41% of the total land

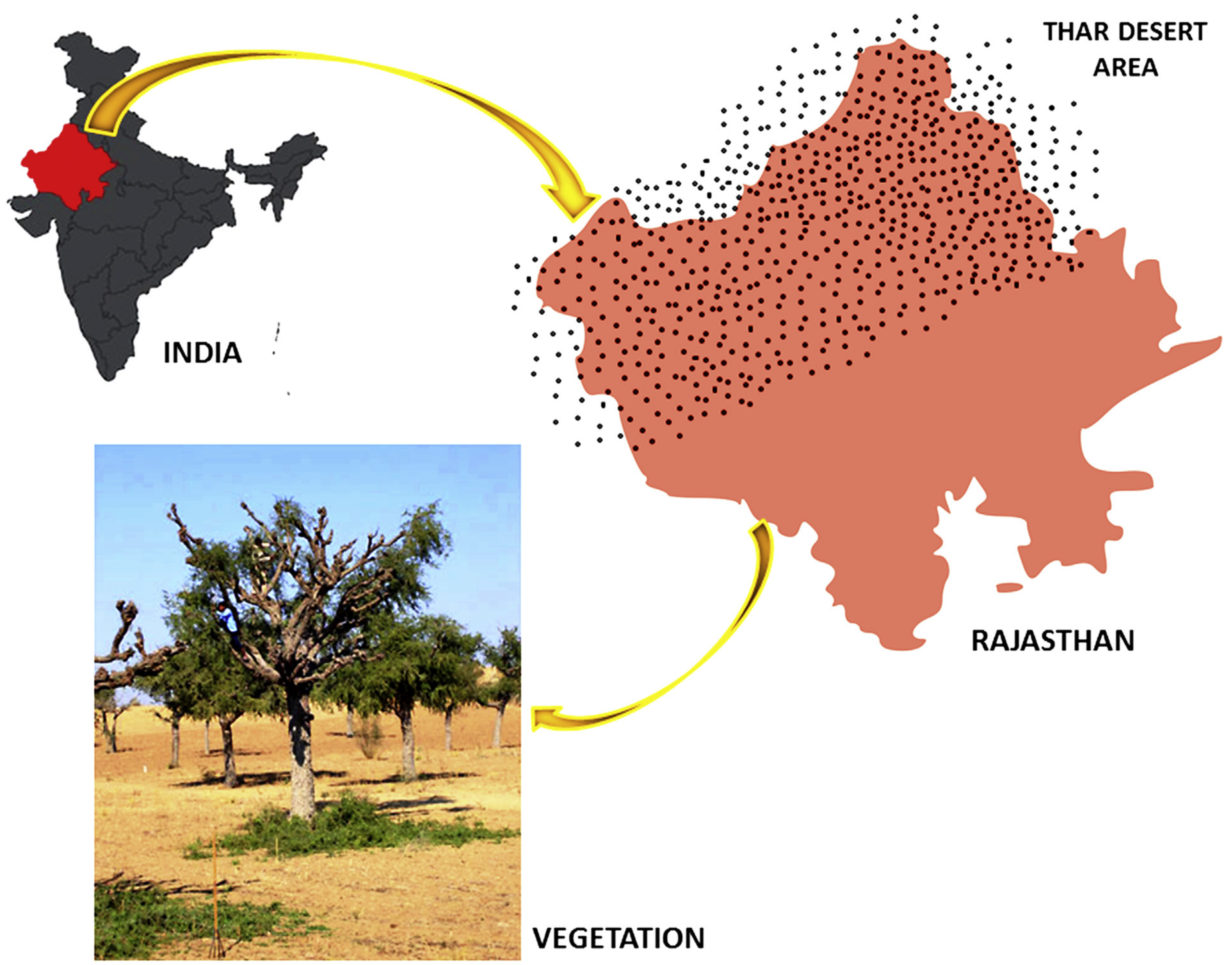


Fig. 1. Map of India showing location of the Thar Desert (doted area) in Rajasthan and their vegetation.

area of India. The Thar Desert occupies the highest proportion of the land of the Rajasthan than other major physiographic regions of Rajasthan that is, the Aravalli hills, the Eastern plains, and the South-Eastern plateau [2]. The Great Indian Thar Desert lies between 25′ 2 to 28′ 10 N and 69′ 3 to 74′ 0 E over North-Western parts of Rajasthan with an area of around 25,000 km^2 comprise the arid and semi-arid region of Jodhpur, Jaisalmer, Bikaner, and Barmer districts (Fig. 1).

The majority of the land is made up of dry undulating plains of the hardened sand tracts whereas the rest of the land is mainly covered from sandy and sandy loam soils. The climate of this region is characterized by low humidity, sandstorm, less precipitation (the average annual rainfall ranges from less than 100 to 400 mm), and extremes of diurnal and annual [12]. The Rajasthan has rich floral diversity with 911 wild species belonging to 780 genera of 154 families [2]. The Thar Desert exhibits a broad array of habitats and biodiversity of flora and fauna. Dry open grasslands with interspersed thorny bushes and trees make the major portion of the flora of the Thar Desert. This type of vegetation comprising thorny, prickly, and stunted shrubs or perennial herbs or the trees, maybe categorized as thorn forest type or scrub forest type. 58% land of the desert is covered by sand dunes. Some of the plants that commonly constitute the vegetation of the Thar Desert are the *Capparis decidua* (Forssk.) Edgew., *C. procera*, *Calligonum polygonoides* L., *Acacia senegal* (L.) Willd., *Prosopis cineraria* (L.) Druce, *Aerva javanica* (Burm.f.) Juss. ex Schult., *Aristida adescensionis* L. [1], *Acacia jacquemontii* Benth., *A. nilotica*, *C. polygonoides*, *C. decidua*, *Commiphora wightii* (Arn.) Bhandari, *Leptadenia phytotechnica*, *Lycium barbarum* L., *P. cineraria*, *S. oleoides*, *S. persica*, *Tamarix aphylla* (L.) H.Karst., and *Zizyphus nummularia* (Burm.f.) Wight & Arn.. Herbs and shrubs like *Aerva persica* (Burm.f.) Merr., *Blepharis scindica* Stocks ex T.Anderson, *C. procera*, *Crotalaria burhia* Buch.-Ham. ex Benth., *Cymbopogon javarancusa* (Jones ex Roxb.) Schult., *Euphorbia caducifolia* Haines, *Grewia tenax* (Forssk.) Fiori, and *Tephrosia purpurea* (L.) Pers. can generally be observed on the rocks and sandy ridges [13,14].

3. Isolation of endophytic fungi from desert plants

Endophytic microflora has been isolated from a wide array of plants ranging from mosses to trees. Aboveground plant parts, as well as belowground plant parts have been proved to be possible niches to harbor the endophytic microflora. Plant samples like leaves, stem, and roots should be collected from healthy symptomless plant to be studied and then processed within 24 hours of collection or can be stored at 4°C in iceboxes and processed within 48 hours of collection. Before the processing of the samples, they should be washed thoroughly under running tap water to remove debris and the dirt on them. Then samples were surface sterilized by using the most common procedure used for surface sterilization which may vary from plant to plant. This surface sterilization or the sanitization of the plant sample surface by using disinfectant is required to confirm that isolated microorganisms are endophytes, not epiphytes [15].

The surface sterilization is started by repeated washing with sterile distilled water for 4-5 times followed by immersing the plant tissue in 70–75% ethanol for a few minutes. Then again wash with sterile distilled water followed by eventually immersing in sodium hypochlorite with 4% chlorine, and ethanol for few minutes separately. After the successive washing with disinfectants finally rinse with double distilled water (DDW) and then place in sterile and dry condition then cut into small pieces. These small pieces should be placed on appropriate growth media e.g. potato dextrose agar (PDA) for fungus, nutrient agar for bacteria, and starch casein agar (SCA) medium for actinomycetes. The remaining rinse water after the final washing of the sample can be used as a control to check the efficacy of the surface sterilization. If there is no microbial growth on the plate inoculated, then it indicates successful surface sterilization of the plant sample. Fig. 2 represents step by step procedure of endophyte microflora (isolation to identification). Wide arrays of the diversity of endophytic fungus/bacteria have been identified to be isolated from the plant growing in the desert area. Endophytes are known

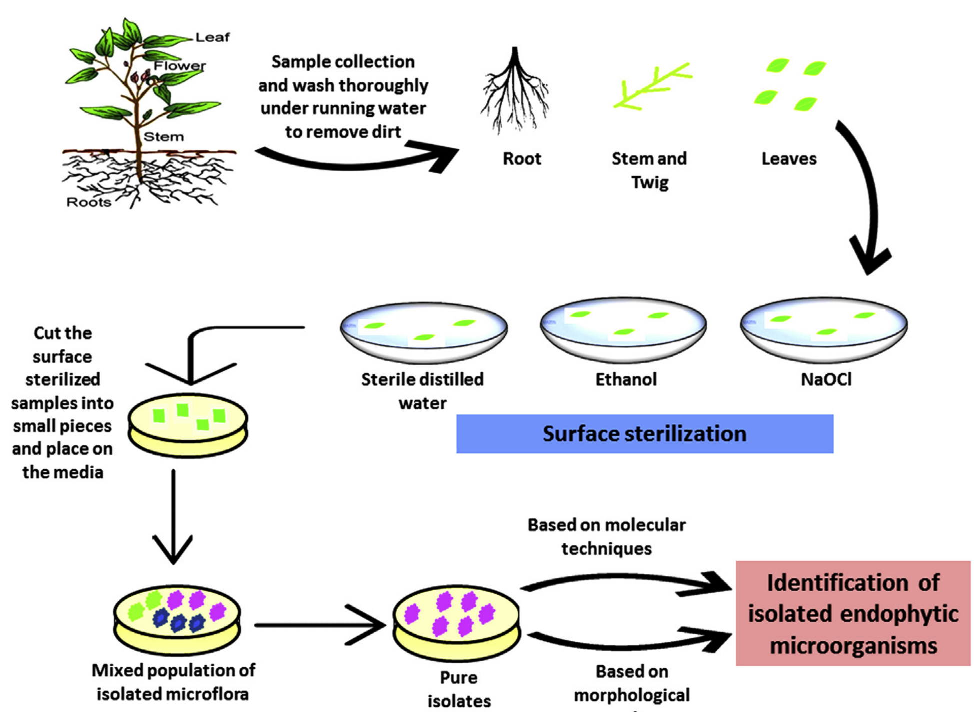


Fig. 2. Isolation and identification procedure of endophytic microflora.

to possess several beneficial traits for plants like secondary metabolite production that promotes plant growth, provides protection from pathogens and abiotic stress, and also facilitates the uptake of nutrients [16].

4. Transmission of endophytic fungi

Dissemination of microorganisms within and among the host community is defined as transmission. Endophytic microflora exhibit two modes of transmission, one is the horizontal transmission and another is the vertical transmission. The former mode involves the transmission by means of sexual or asexual spores and later one involves the transmission from the host to their offsprings by means of host tissues such as seeds and vegetative propagules [8]. In vertical transmission, endophytes transmit from one generation to the next generation of the selfsame host plant through a pre-inoculated parent plant which develops a systemic infection in progeny. Such types of endophytic microorganisms are known as systemic endophytes since they produce systemic infection throughout host plant tissues. Endophytes that reside within the grasses are predominantly reported to exhibit such types of mode of transmission and infection [17].

In horizontal transmission, the transfer of inoculum of endophytes takes place between one host plant to another compatible host plant [18]. This kind of endophytes identified as non-systemic endophytes which chiefly colonizes most of the woody plants and some grasses. Horizontal transmission produce highly localized infections within the leaf, petiole, bark, or stem of the host plant that has been got infected through endophyte inoculums [19,20,21,22]. Endophytes possibly may produce sexually or asexually [191]. Unlike the vertical mode of transmission, the horizontal mode of transmission is independent of host plant parts such as host seeds or vegetative parts for the dissemination of inoculums of endophytes [19,23]. Neotyphodium and few endophytic fungi are transmitted *via.* the vertical mode of transmission through infested seeds. Sometimes spores of vertically transmitted endophytic fungi may transfer *via.* the horizontal transmission to the hosts [24]. Nearly all of the endophytic fungi reported are latent saprophytes whereas some of them are identified as latent pathogens [209]. The inoculums of most of the endophytes being saprophyte, may infect new host plants after the death of host/tissue, therefore, in horizontal transmission, debris of the host plant might serve as a prominent source of endophytic inoculums [25,209].

Herbivorous insects also transmit fungal spores of endophytes among host plants through their fecal pellets since spores of several species of fungi are identified to be resistant for gut digestion [26,27]. Conidia liberated from conidiophores exhibit horizontal transmission among plant communities through rain or dew [210]. Petrini [28,29] stated that colonization of endophytes is the result of several events owing to host-endophytes interactions such as the arrival of endophytic inoculum on the host plant, identification of suitable host, germination of spore, penetration of the epidermal layer, and tissue colonization of plant part of the host. Fungal endophytes can colonize host plants *via.* immediate invasion of plant tissues by using hyphae or through particular infection structures such as appressoria [30,31]. In planta, colonization might be either widespread or scanty [32,33]. Like endophytic fungi, bacterial endophytes also exhibit horizontal as well as vertical modes of transmission. However, it has been considered that an obligate association between bacteria and plants is not ferquently found. Generally, indirect vertical mode of transmission is reported where the vertical transmission of endophytic bacteria from seed to reproductive organs of the host plant is not documented yet. There are some studies indicated that some bacterial endophytes of seeds perform mixed modes of transmission. There is evidence that transmission through colonization of roots is more frequent in the bacterial endophytic communities than aerial transmission [34].

5. Biodiversity of endomicrobiome of plants

It has been reported that each group of plants from thallophytes to spermatophytes and from hydrophytes to xerophytes harbor endophytic microbiota [35–37]. Endophytes like fungus, bacteria, and actinomycetes have been found as the most useful and greatly diverse group of microbiota to reside within the plants of the different part of the globe, such as rainforests [38], oceans [39], mangrove swamps [40], Arctic [41], Antarctic [42], coastal forests [43], geothermal lands [44], and deserts [45]. They also have been isolated from ferns, gymnosperms, and angiosperms of the tropical forests, diverse xeric climates, extreme arctic flora, and boreal forests [46,47]. There are myriad reports indicates that diversified environmental conditions comprising drought [32,33], low temperature [48], elevated temperature [49–51], high salinity [52], and multiple extreme conditions [35–37,53] are responsible for niche-specific diversity of the microbial community. Moreover, the term endophyte is a topographical term that comprises all the organisms that asymptomatically reside within the living internal tissues of the plant parts of the host at any stage of their life. Almost all vascular plant species have been studied so far to be colonizing by endophytic microbes [6].

According to some reports, a highly diverse community of endophytic fungi is found in the tropical [54] while others depicted contradictory outcomes [55,203]. A number of fungal species and their composition in isolated endophytic communities recovered from the host may vary with the sterilization protocol and isolation media have been used [56]. Hence, the diversity of endophytic community is greatly influenced by the sample size, sterilization protocols, isolation techniques, and cultural media used. Endophyte array also seems to be certain at the host species or tissue level but species constitutions and their frequencies are considerably affected by the site-specific scenario [57,58]. Numerous reports have been presented to manage the sterilization methods, cultural conditions, and procedures for endophyte diversity assessment [56]. A sampling of the host tissue has a profound effect upon the correct estimation of the endophytic diversity of the host plant, thus sampling of host tissue from distinct geographical areas, incorporation utmost type of plant part tissues, sample size, and season of the sampling remarkably improve the endophytic diversity assessment of the plant to be studied for [32,33].

Fungal endophytes have been reported from nearly all plant parts inclusive of root, stem, bark, twig, leaf, petiole, flower, and seed [59]. Endophytic diversity in the host plant is also affected by the age of the host plant itself [60]. Generally, woody plants have a broad range of endophytes than grasses; thus, led to less host specificity of endophytes [28]. In spite of that, at the same time, Petrini et al. [208] stated that endophytes of several woody plants are anticipated to be very specific at the host-species level. Fungal species belongs to the subdivision Ascomycotina are the most commonly reported fungal endophytes followed by Basidomycotina and Zygomycotina [61]. Fungal endophytes can be described under two groups Clavicipitaceous (C) endophytes and Non-clavicipitaceous (NC) endophytes on the basis of taxonomy, evolutionary relations, plant hosts, and ecological activities [19,28,56,62,199].

Endophytic fungi recovered from grasses falls under the group C-endophytes whereas those belonging to a different range of species from Ascomycotina, and Basidiomycotina reported from nearly all plant species of the temperate and tropical zones including grasses falls under the group NC-endophytes [56,63].

NC-endophytes further characterized into four classes by Rodriguez et al. [200] on the basis of host colonization pattern, mechanism of transmission between hosts, biodiversity of endophytic community within the host, and ecological importance. First-class includes the fungal endophytes of phylogenetically related clavicipitaceous species with limited host range and is restricted to grasses. Whereas, fungal endophytes of class second, third and fourth are non-clavicipitaceous species with a wider host range. Among them, class second is known to colonize both phyllosphere and rhizosphere whereas class third, and fourth is restricted to phyllosphere and rhizosphere, respectively [64]. In the case of bacterial endophytes, a total of sixteen distinct bacterial phyla have been discovered, among them, the majority of species fall under the phyla Actinobacteria, Firmicutes, and Proteobacteria [195]. Some potential colonizing groups such as Clavibacter, Cellulomonas, Curtobacterium, and Microbacterium have been characterized as endophytes by using 16S rRNA gene-based techniques. These endophytic bacterial phyla have been accounted for the major portion of bioactive molecules such as naphthomycins, clethramycin, kakadumycins, munumbicins, and others, which synthesized by endophytic bacteria [201]. *Kitasatospora* sp. a bacterial endophyte of *Taxus baccata* has been reported for the production of paclitaxel [65].

Around 300,000 higher plant species cover the earth's surface, and according to previous reports revealed that each species harbor either one or an abundance of endophytic microflora within them. Out of these plant species that present on the globe, only a few dozen, have been studied so far for their endophytic microbial community [8,66]. Considering this rationale and also the fact that since the flora of the Great Indian Thar Desert is full of ethnopharmacologically important plants have been studied so far for their endophytic community and their biopotential, therefore, endophytic diversity of some medicinally important plants of the Thar Desert will be discussed in this section.

6. Host-endophyte interactions

Plant-fungal association is known to be as old as plants come into existence. This association may exist in a balanced (endophytes, mycorrhiza) or unbalanced manner (pathogen). There is a very fine line exists between pathogenicity and endophytism. A fungal endophyte establishes a balanced association within the host plant. Schulz and Boyle [62] put forward that asymptomatic colonization of endophytic fungi owed to the equilibrium of antagonism between fungal virulence and plant defense where fungi exhibit a degree of virulence for food and shelter, colonization, and nutrients access, in turn, host plant limit the fungal colonization through defense mechanism. Disruption in this balance might leads to fungal disease development in the host plant due to some factors related to the host such as nutrient deficiency, age, plant death, or any environmental factors. These fungal endophytes become saprophytes upon the death of the host plant. In this mutualistic interaction between the host plant and the fungal endophyte, endophytic fungi receive nutrition and shelter from the plant while the host plant gets enhanced resistance to numerous abiotic and biotic stresses [67].

Some researchers believed that this symbiotic relationship can be a protective mutualism where endophytes defend their host plants towards herbivory, consequently protecting their own resources [68]. Wilkinson and Sherratt [69] stated that the most ecologically important mutualism involves the horizontal transmission and a diverse array of symbionts [70]. Yuan et al. [206] proposed that endophytic fungi enhanced plant nutrient availability, stress tolerance, and metabolism. Endophytic fungi have an impact on the diversity of plant community, population characteristics, and ecosystem. The fungal endophyte research got global attention after the first observation of toxicity in cattle grazing on fungal infected grasses in the European countries in the middle of the 20th century. The toxicity in the grazing animals was considered due to the alkaloids produced by intercellular symbionts belonging to clavicipitaceous members of Ascomycotina. A number of reports have shown that these alkaloids can negatively affect a wide variety of invertebrate and vertebrate herbivores and pests [71]. Furthermore, endophytic fungi not only enhanced plant growth but also increased resistance against a broad range of biotic and abiotic stresses. Possibly, due to the synthesis of plant growth regulators, perennial ryegrass infected with endophytic fungi grew considerably faster than ryegrass without endophyte [72]. Endophytes may play an important role in some plants to cope with drought conditions [27]. Lewis [73] studied the impact of endophytic fungus, *Neotyphodium lolii* under biotic or abiotic stresses (shade, low pH, low nitrogen, and cutting) on plant growth and observed that the dry weight of infected plants was 10% more than uninfected. Enhanced abiotic stresses tolerance in tall fescue due to endophytic symbiosis are not universal in expression, and the mechanisms by which the symbiosis imparts such benefits are not much explained yet.

Plant responses to endophytes involve a combination of complex physiological, biochemical, and morphological adjustments governed by host genotype, endophyte genotype, environment, and their interactions [74]. Endophytes are considered to affect the osmotic potential and recovery capability of endophytic infested grasses since the accumulation of carbohydrates such as glucose; fructose, arabitol, and mannitol have been reported in infected grasses under drought stress [75]. Furthermore, endophytes also provide tolerance to soil aluminum toxicity, phosphorus poor soil, low or high mineral stresses, and low soil pH [76]. Several workers observed *in vitro* inhibition of the growth of plant pathogens by endophytes [205]. Endophytic bacteria possess the capacity to synthesize the pharmaceutically important secondary metabolite of their host origin as well as novel bioactive molecules such as terpenes, alkaloids, steroids, phenols, quinones, tannins, and saponins. Some bacterial endophytes have also been identified to facilitate the increased plant defense mechanism and the nutrient uptake of their host plant. These bacterial endophytes affect plant growth either directly by enhancing the level of plant growth promoters or indirectly by assisting in nutrient uptake [65].

7. Endomicrobial diversity of important medicinal plants/genus

Calotropis gigantea and *C. procera* are the two important members of the genus *Calotropis* (Asclepiadaceae). These are widely used as medicinal plants in the Indian subcontinent. *C. procera* is a small wild-growing tropical plant, known by different names like Sodom apple, usher, Dead Sea apple, swallow wart, milkweed, giant milkweed, Aakanda, and Madaar of India [77]. It is a xerophytic shrub growing widely in the arid and semiarid area, with a height of 6 meters. It flourishes well without irrigation, chemical fertilizers, and other agricultural practices [78]. The plant is the constituent of many Ayurvedic formulations like Arkelavana. Ethnomedicinal properties of plant extracts and pure compounds of *C. procera* have been very well known to traditional systems of medicine since time immemorial. It has been traditionally used to cure diarrhea, stomachic, sinus, fistula, jaundice, and skin disease [189,190]. *Calotropis gigantea* is also one of the most important medicinal plants in India [79–82]. It is a small shrub with 4 m in height. It has been known to cure leprosy, elephantiasis, asthma, chronic rheumatism, piles, ulcer, and skin diseases, since it possesses cardiotoxic, emetocathartic, cytostatic, abortifacient, digitalis, antimalarial, and antimicrobial properties. Both species of *Calotropis* were exploited for endophytes as a possible source of bioactive compounds.

A total of 12 endophytic fungi six from hyphomycetous, four from coelomycetous, one from Ascomycetous, and one from sterile mycelia producing form have been isolated from the 700 segments of the flower, leaves, and stem of *C. gigantea viz. Alternaria porri*, *Aspergillus flavipes*, *Fusarium oxysporum*, *Nigrospora sphaerica*, *Aspergillus niger*, *Curvularia lunata*, *Colletotrichum falcatum*, *Phomopsis archeri*, *Pestalotiopsis sydowiana*, *Phoma exigua*, and *Leptospharulina chartarum* [83]. In another study, four endophytes species namely, *Alternaria* sp., *Aspergillus* sp., and *Cladosporium* sp. isolated from root, stem, and leaf segment of *C. procera* [84] have been identified 5 endophytic fungi, three from the stems and two from the roots of the *C. gigantea* as *Phomopsis asparagi*, two strains of *Colletotrichum gloeosporioides*, *Calonectria eucalypti* and *Xylaria* sp. It has been observed that age and developmental stage of the segment of plant part also affect the colonization frequency of isolated endophytic microflora for example a total of 156 endophytic fungi belonging to 19 different taxa that are *Acremonium kiliense*, *Acremonium strictum*, *Cercospora pulcherrima*, *Cladosporium cladosporioides*, *Cladosporium oxysporum*, *Colletotrichum gloeosporioides*, *Curvularia pallescens*, *Diplodina microsperma*, *Glomerella cingulata*, *Guignardia bidwellii*, Hyphomycete, *Microascus desmosporus*, Mycelia sterilia (Morphotaxon 1), Mycelia sterilia (Morphotaxon 2), Mycelia sterilia (Morphotaxon 3), *Phaeoramularia calotropidis*, *Rhodotorula glutinis*, *Xylaria* sp. have been recovered from 468 segments of *C. procera* leaves of different age and developmental stage.

The highest number of fungal isolates and species were obtained from the old leaves which indicate that colonization frequency increased with increasing leaf age [85]. About 9 different fungal strains have been discovered from the leaf samples of *C. gigantea*. Identification of the fungal strains based on the type of colony, reproductive structure, and internal transcribed spacer (ITS) region analysis revealed that the predominant fungal strains belonged to the species *Aspergillus*, *Phoma*, and *Penicillium* [86]. Verma et al. [35–37] found *Aspergillus niger* to predominant fungal isolates among 14 endophytic isolates from the root of the *C. procera*. Chowdhury et al. [84] identified and characterized four endophytic fungi by 18S rRNA sequencing approach namely, *Pencillium* sp., *Aspergillus* sp. [155]. *Alternaria* sp. and *Cladosporium* sp. from the plant parts of *C. procera* with the colonization frequency of 33.33% for *Alternaria* sp. 16.66% for *Penicillum* sp. and 8.33% for *Aspergillus* sp., and *Cladosporium* sp. [84,87,88].

A total of 13 endophytic fungi namely, *Aspergillus niger*, *Aspergillus flavipes*, *Alternaria porri*, *Curvularia lunata*, *F. oxysporum*, *Nigrospora sphaerica*, *Colletotrichum falacatum*, *Pestalotiopsis sydowiana*, *Phoma exigua*, *Phomopsis archeri*, *Leptosphaerulina chartarum*, and Mycelia sterilia have been recovered from 700 segments of the plant parts of 10 plants of *C. gigantea* and were identified by means of colony and reproductive structures [83]. Some endophytic fungi also have been recovered from the latex of the *C. procera*. Eight fungal species belonging to the genera *Aspergillus*, *Fusarium*, *Penicillium*, *Emericella*, *Nigrospora*, and *Trichoderma*have been discovered from the latex and the leaves of *C. procera* [77,89]. A total of 8 endophytic fungi comprising *Aspergillus flavus*, *Penicillium sublateritium*, *Phoma chrysanthemicola*, *Phoma hedericola*, *Candida albicans* along with some commonly found endophytic fungi *viz. Aspergillus niger*, *Aspergillus*sp., *Phoma*sp. were discovered from 473 segments of *C. procera*. There were no endophytic fungi were observed in 118 segments from the leaf samples [90]. *Myrothecium verrucaria*, *Alternaria alternata*, *Epicoccum nigrum*, and *Aspergillus terreus* were identified as endophytic fungi of *C. procera* by El-Khawaga et al. [91]. A study conducted by [92] reflected that *A. flavus*, *Chaetomium globosum*, *Cochliobolus lunatus*, *Fusarium dimerum*, *F. oxysporum*, and *Penicillium chrysogenum* were the most prevalent endophytic fungal species among 161 isolates belonging to thirty-three different taxa from the leaves of *C. procera*.

7.1. Endomicrobial diversity of Calotropis spp

Withania somnifera is an important tropical medicinal plant that belongs to the family Solanaceae, also known as Ashwagandha (English name: winter cherry) or Indian Ginseng has traditionally been used in traditional medicine systems like Ayurveda, Siddha, Unani and Chinese. It has been known that 91 pharmaceutical products comprising active steroidal lactones withanolides, withanolide-A, and withaferin-A as major bioactive molecules obtained from roots, stem, bark, leaves, flowers, and seeds of the *W. somnifera*. It possesses a broad spectrum of therapeutic activities like anti-hyperglycemic, neuropharmacological, immunomodulatory, cardioprotective, musculotropic, hepatoprotective, radiosensitizing, chemoprotective, anti-aging, macrophage-activating, diuretic, hypocholesterolemic, aphrodisiac, rejuvenating, and hemopoietic [93], anti-leukemic, anti-invasive, anti-metastatic, apoptotic, anti-inflammatory, radiosensitizing and antidiabetic activity anticancer, antistress, antitumor, antibiotic, anticonvulsant, CNS depressant, aphrodisiac, liver tonic immunomodulatory and insect anti-feedant activity [94].

The therapeutic potential of *W. somnifera* is due to its endophytes. A total of twenty-nine endophytic fungi belongs to 16 different genera of phylum Ascomycota and Zygomycota namely, *Aspergillus* sp., *A. niger*, *A. restructus*, *Fusarium acutatum*, *Fusarium armeniacum*, *Fusarium avenacium*, *Fusarium begoniae*, *Fusarium dimerum*, *Fusarium oxysporam*, *Fusarium redolens*, *Fusarium sambusinum*, *Fusarium semitectum*, *Fusarium solani*, *Fusarium udum*, *Fusarium verticilloides* and *Mucor* sp. were isolated and identified from the root of *W. somnifera* with the colonization frequency of 35% [95]. Atri et al. [96] isolated twenty-four fungal endophytes from *W. somnifera* during the rainy season of which ten isolates from the stem with the highest colonization frequency (CF) of 41.66% followed by nine from the root with 37.50% CF and five isolates from the leaf with 20.83% CF. Among them, two fungal isolates were identified as *Alternaria* sp. and *Fusarium* sp.

7.2. Endomicrobial diversity of Solanum spp.

Solanum is a medicinally important genus belonging to the family Solanaceae. *Solanum nigrum* and *S. surattense* are the two most common species in this genus used in the traditional medicine system. It is a common herb or perennial shrub of 1 to 2 feet high erect, angular branched stem with dark green, ovate, and wavy toothed or nearly entire leaves. It grows in tropical and subtropical regions throughout the globe. Traditionally, it has been used to cure fever, allay pain skin problems, tumors wounds, and cancerous sores, various diseases of lungs, urinary tract, gall bladder, and rheumatism over the years. The potency of *Solanum* sp. can be attributed to the endophytes (fungi or bacteria), which produces a wide array of metabolites with high medicinal implications. A total of 16 endophytic fungi belonging to ten different genera were isolated from leaf samples of *S. nigrum* by using agar plates and moist chamber plates. *Penicillium digitatum*, *Aspergillus awamori*, *Alternaria* sp. was recovered from leaf tissues in a moist chamber whereas *Torula herbarum*, *Trichoderma harzianum*, and *A. flavus* isolated from leaves in agar plates [97]. Khan et al. [98] reported two endophytic fungi *Fusarium tricinctum* and *A. alternata* from the leaves of *S. nigrum*. Endophytic bacteria namely, *Serratia nematodiphila*, *Enterobacter aerogenes*, *Enterobacter* sp. and *Acinetobacter* sp. were recorded from plant parts of *S. nigrum* L. [194]. Some endophytic fungi are also isolated from the fruit and stem of *S. nigrum*. For example, three endophytic fungi, *Aspergillus* sp., *Aspergillus* sp., and *Lasiodiplodia theobromae* were recorded from stems, leaves, and fruits of *S. nigrum* L. [99].

Eight fungal endophytes were recorded from the leaves and unripe fruits of *Solanum mauritianum* and were identified by using morphological traits and ITS-rDNA method namely, *Aureobasidium pullulans*, *Paracamarosporium leucadendri*, *Cladosporium* sp., *Collectotrichum boninense*, *Fusarium* sp., *Hyalodendriella* sp., *Talaromyces* sp., and *P. chrysogenum* [100]. In another study, conducted by Pelo et al. [100], endophytic fungi *P. chrysogenum*, *Fusarium* sp., and *Paracamarosporium leucadendri* have been isolated from the leaves and unripe fruit of a healthy plant of *Solanum mauritianum.* These fungal isolates have been identified by using ITS rDNA sequencing where outcomes of the phylogenetic analysis depicted different clustering of the fungal isolates at 94–100% similarities. Ikram et al. [101] have isolated two endophytic fungi *Penicillium roqueforti* and *Trichoderma reesei* from the root tissues of *S. surattense.* The characterization of these potent fungal endophytes has been done on the basis of morphological as well as molecular ITS-based sequencing analysis [101].

7.3. Endomicrobial diversity of Aloe vera *L.*

Aloe vera L. is the succulent evergreen plant, distributed in the tropical regions of the globe. It is a medicinal, herb widely known for its significant traditional usage and commercial importance in the field of cosmetics, tonics, and the food industry. Approximately 75 natural products are produced by *Aloe vera* [102]. It exhibited high inhibitory activity against elastin and α-amylase activities, and mild inhibition on neuraminidase and lipase activities [103]. A total of 129 bacterial endophytes representing ten genera grouped into four classes were isolated of which thirty-two isolates were identified on the basis of genetic similarity namely, *Enterobacter* sp. (4), *Enterobacter asburiae* (1), *Enterobacter tabaci* (8), *Enterobacter ludwigii* (4), *Pantoea agglomerans* (1), *Pantoea cypripedii* (1), *Lelliottia nimipressuralis* (1), *Paraburkholderia* sp. (1), *Bacillus megaterium* (3), *Bacillus agri* (1), *Lysinibacillus xylanilyticus* (1), *Lysinibacillus macroides* (2), *Microbacterium aerolatum* (1), and *Chryseobacterium taiwanense* (3) from roots of *Aloe vera* [102]. Three endophytic bacteria *Bacillus cereus*, *B. licheniformis*, and *Lactobacillus paralimentarium* and one endophytic fungus *Yeast*: *Clavispora lusitaniae* were recorded from gel from leaves of *Aloe vera* [104]. Apart from root and gel from leaf, a total of thirty-eight fungal endophytes belonging to Ascomycetes class and three subclasses of filamentous fungi that are Chaetomiaceae, Hypocreaceae, and Trichosphaeriaceae, have been isolated from sixty-two segments of the inflorescence of *Aloe vera* with 61.3% colonization frequency. *Chaetomium* (42.1%), and *Trichoderma* (28.9%) were identified as predominant genera among other isolates [105]. A total of sixteen endophytes recorded from 50 segments of the root of *Aloe vera* were identified as *F. oxysporum*, *Nigrospora* sp., *A. alternata*, *Aspergillus* sp., and *Penicillium* sp. [106].

Akinsanya et al. [107,108] have been employed distinct high throughput techniques by assessing PCR amplicon of 16S rDNA sequences (V3–V4 regions) of bacterial endophyte recovered from root, stem, and leaf tissues of *Aloe vera* with the Illumina metagenomics technique for the identification of the isolates. The outcomes of analyses exhibited Proteobacteria, Firmicutes, Actinobacteria, and Bacteriodetes as the predominant genera. In addition to this, another yellow Gram-stain-positive, non-motile, non-endospore forming, spherical endophytic actinobacterium reported from fleshy tissues of the leaf of *Aloe barbadensis* (*Aloe vera*) which was further identified as novel species of the genus *Micrococcus* that is *Micrococcus aloeverae* sp. nov., with strain AE-6 T (5MCC 2184T5DSM 27472 T) by using high throughput techniques like 16S rRNA gene sequencing and MALDI-TOF/MS [109]. Akinsanya et al. [107,108] isolated twenty-nine endophytic bacteria from the root, stem, and leaf tissues of *Aloe vera*, which fall under the thirteen genera of bacteria i.e. *Pseudomonas*, *Bacillus*, *Enterobacter*, *Pantoea*, *Chryseobacterium*, *Sphingobacterium*, *Aeromonas*, *Providencia*, *Cedecea*, *Klebsiella*, *Cronobacter*, *Macrococcus* and *Shigella* [107,108]. Sixteen fungal endophytes have been isolated from the root of *Aloe vera* are associated with *F. oxysporum*, *Nigrospora* sp., *A. alternata*, *Aspergillus* sp., and *Penicillium* sp. [106].

7.4. Endomicrobial diversity of genus Ocimum

Ocimum genus belonging to the family Lamiaceae family comprises more than 150 species includes *Ocimum basilicum* L., *Ocimum sanctum*, *Ocimum canum* L., *Ocimum gratissimum* L., and *Ocimum minimum* L. It has been found throughout the world. It is a worldwide famous herb for its wide array of applications due to the presence of a broad range of bioactive molecules. It is known for its medicinal properties such as carminative, galactagogue, antispasmodic, antimicrobial, antioxidant, anti-inflammatory, anticancer, antidiabetic, anti-allergic, antipyretic, anti-asthmatic, and analgesic properties thus used to cure headaches, coughs, diarrhea, worm, and kidney infections. Fourteen fungal endophytes representing eight genera comprising *Aspergillus*, *Ascochyta*, *Nigrospora*, *Blastomyces*, *Colletotrichum*, *Exidia*, *Clitopilus*, and *Nomuraea* were recorded from the *Ocimum basilicum* var. *thyrsiflora* [110]. Taufiq and Darah [111] identified *Lasiodiplodia pseudotheobromae* IBRL OS-64 as a fungal endophyte that dwells within leaf tissue of *Ocimum sanctum* Linn. In another study, *Paecilomyces variotti* Bain was isolated from the roots tissues of *Ocimum sanctum* Linn. [112].

A novel species of the genus *Mariniluteicoccus* i.e. *Mariniluteicoccus endophyticus* sp. has been reported as bacterial endophytes from the root of *O. basilicum* [113]. L-Asparaginase producing a bacterial endophyte has been reported from *Ocimum tenuiflorum* (Tulasi) which was identified as *Bacillus stratosphericus* by using 16 s rRNA sequencing [114]. Panigrahi et al. [115] obtained *Enterobacter cloacae*, a bacterial endophyte from the stem of *Ocimum sanctum*. Sahu et al. [116] in their study reported twenty-one endophytic bacteria recovered from *Ocimum tenuiflorum*. Among them, eight bacterial endophytes with potential antimicrobial activity have been identified as *Bacillus altitudinis*, *Bacillus tequilensis*, *Bacillus safensis*, *Bacillus haynesii*, *Bacillus paralicheniformis*, *Bacillus pacificus*, and *Bacillus siamensis* [116].

7.5. Endomicrobial diversity of genus Salvadora

Salvadora is a small genus from the family *Salvadoraceae*, mainly comprises evergreen trees or shrubs dispersed in the arid or semiarid environments of Asia and tropical Africa. It is known as Pilu in Rajasthan. *S. persica* is well known for its ethnobotanical uses and oral hygiene. It is small with 6–7 m height branched shrub possesses greenish small leaves having an instance aroma of cress or mustard, greenish-yellow flowers, and small red fruits when ripe. It has been used to cure various disease ailments such as piles, urinary disorder, rheumatism, skin diseases, seasonal cough and cold, diabetes, asthma, gout, constipation, and respiratory infections [117].

It has been believed that some endophytic fungi show strictly tissue specificity. In a study *A. flavus*, *A. fumigates*, *A. ochraceus*, *A. oryzae*, *A. parasiticus*, *A. ustus*, *A. wentii*, *A. niger*, *A. ochraceus*, *Cladosporium herbarum*, *Aspergillus* sp., *E. nigrum*, *Fusrium moniliforme*, *Neosartorya glabra*, *P. chrysogenum*, *Stachybotrys atra*, *Trimmatostroma*sp. and unidentified fungus were recorded from fresh and healthy leaves and stem samples of *S. Oleoides* of which only 4 species showed tissue specificity. *F. moniliforme*, *Trimmatostroma* sp. were restricted to stem only whereas *Aspergillus*sp., *C. herbarum* to leaves only [118]. A total of 35 isolates of endophytic fluorescent *Pseudomonas*were identified from the leaves, shoot,

Table 1
Endophytic microflora of ethnomedicinal plants of the Thar Desert and their biopotential.

Plant	Plant parts	Ethnomedicinal uses of plants in Rajsthan	Bacteria	Fungus	Bioactive molecule	Pharmaceutical activity	References
Solanum nigrum L.	Stems, leaves and fruits	Fruit cut in lengthwise, filled with purified butter is eaten in cough and cold. Decoction is taken orally thrice a day for 3 day to cure from fever. The fruits are eaten against diarrhea, hydrophobia and conjunctivitis. It is kept in eye and made rounds clockwise and anticlockwise to remove foreign body from eye. Leaves are cooked as vegetable and eaten to treat sprain, swelling and rheumatism. Dried root is rubbed on stone and applied against snake bite.	*Sphingomonas* sp. and *Pseudomonas* sp.	*Aspergillus* sp., *Aspergillus* sp., *Lasiodiplodia theobromae*, *Penicillium digitatum*, *Aspergillus awamori*, *Torula herbarum*, *Trichoderma harzianum*, *Aspergillus flavus*, *Cladosporium herbarum*, *Aspergillus niger*, *Monascus* sp., *Penicillium citrinum*, and *Penicillium chrysogenum*	Indole compounds, Sapinofuranone B, Solamargine, Ergosterol, Ergosterol peroxide, Indole-3-carboxylic acid (ICA), Indole-3-acetic acid (IAA), Penicelcyclo(leu-pro), and Cyclo(Phe-Pro)lic acid, 3-Indolaldehyde, Γ-Lactone, Diketopiperazine, etc.	Cytotoxic	Katewa et al. [135]; Jain et al. [136]; Upadhyay et al. [204]; Chen et al. [137]; Nayak [97]; El-Hawary et al. [138]; El-Hawary et al. [196]; Abdallah et al. [184]
Solanum surattense Burm. f.	Roots	Affected part is fumigated to cure piles by smoke treatment. To cure from cough one tea spoon powder is taken orally with water for 3 days.	-	*Penicillium roqueforti* and *Trichoderma reesei*	Ferulic acid, Cinnamic acid, Quercetin, Rutin, Alkaloids, Favonoids, Phenols, Steroids, and Tannins	Antibacterial and antioxidant potential	Katewa et al. [135]; Ikram et al. [101]
Phyllanthus niruri L.	Roots and shoots	Useful in hepatitis and jaundice. Fresh root is used for the treatment of viral hepatitis. Leaves mixed with salt applied locally to skin affections, swelling and ulcers in the form of poultice.	New taxa related to *Streptomyces*	*Fusarium* sp., *Chaetomium* sp., and *Colletotrichum* sp.	1,8-Dihydroxy-3-methoxy-6-methylanthracene-9,10-dione, 1,3,8-Trihydroxy-6-methoxyanthracene-9,10-dione, and Dichloromethane	Antimicrobial and antioxidant activities	Khan et al. [197]; Rollando et al. [139]; Yuniati and Rollando [207]; Bhatia et al. [140]; Hannana et al. [141]; Ezzat et al. [185]
Mucuna pruriens (L.) DC.	Roots, stems, seeds and flowers	The seeds are ground with almond, and eaten in case of sexual debility, rheumatism and as tonic. Seed powder is taken with water in summers as a cooling agent and with milk in debility.	-	*Cladosporium*, *Curvularia*, *Aspergillus*, and *Alternaria*	-	-	Upadhyay et al. [204]; Vyas et al. [142]
Justicia adhatoda L.	Leaves	Leaf is useful to cure artritis. Leaves used in amavatik-sula helpful in headache. Whole plant used in tonsilitis.	-	*Aspergillus nomius*, *Glomerella cingulata*, and *Alternaria alternata*	L-Asparaginase	Cytotoxic activity and antimicrobial activity	Jain et al. [143]; Meena and Rao [144]; Upadhyay et al. [204]; Barman et al. [145]; Prabavathy and Phoebe [146]
	Roots and shoots		-	*Chaetomium* sp.	-	Antibacterial activity	Fatima et al. [147]
Ocimum sanctum L.	Stems	Traditionally used in cough. An infusion of leaves is applied externally to the skin in ring worm and other cutenous diseases. Juice of leaves mixed with ginger is given during indigestion. The juice of leaves mixed with black pepper is given in intermittent fever. The leaf juice internally two times a day for 7 days in case of inflamed eyes. Decoction of two leaves with two cloves is taken as antipyretic. Extract of plant is used against liver congestion, pneumonia and bronchitis.	*Enterobacter cloacae* MG00145	*Alternaria tenuissima*, *Colletotricum gloesporioides*, *Diaporthe* sp., and *Trichoderma* sp.	-	Anti-diabetic	Singh et al. [148]; Upadhyay et al. [204]; Kumar et al. [49]; Panigrahi et al. [115]
	Roots and shoots		*Bacillus cereus*	*Lasiodiplodia pseudotheobromae*	-	Antibacterial activity and antimicrobial activity	Nayak and Shashirekha [149]; Tanvir et al. [150];

Table 1 (*Continued*)

Plant	Plant parts	Ethnomedicinal uses of plants in Rajsthan	Bacteria	Fungus	Bioactive molecule	Pharmaceutical activity	References
							Taufiq and Darah [111]
	Roots		-	*Paecilomyces variotti*	-	Hepatoprotective and antioxidant activities	Shukla et al. [112]
Ocimum basilicum var. *Thyrsiflora*	Leaves	To cure respiratory problem. Seed extract increases potency in men.	-	*Nigrospora genus*	-	Antibacterial and antioxidant activity	Jain et al. [143]; Singh et al. [148]; Atiphasaworn et al. [110]
Ricinus communis L.	Roots and shoots	To cure from pneumonia and body pain. Leaves are smeared with Butter or oil, warmed and tied locally to cure headache, muscular pain, colic, nodule in breast, stiffed muscles, boils and pimples. Leaf juice is boiled with Butter and a cotton plug soaked in this mixture is tied on cuts, wounds, boils and pimples to cure completely. Paste of root is smeared over penis against retention of urine	*Enterobacter* sp. and *Bacillus* sp.	*Aspergillus fumigates*, *Aspergillus japonicas*, *Aspergillus niger*, *Fusarium semitectum*, *Curvularia pallescens*, *Phoma hedericola*, *Alternaria tenuissima*, *Fusarium solani*, *Drechslera australien*, and *Aspergillus repens*	-	Antibacterial activity	Singh et al. [148]; Upadhyay et al. [204]; Sandhu et al. [151]; Annapurna et al. [152]
Calotropis procera (Aiton) W.T. Aiton	Roots, shoots and leaves	Flower gynostegium is consumed in diabetes. Flower gynostegium is also usefull in TB and other respiratory diseases. In abdominal pain leaf tied on abdomen.	-	*Aspergillus nomius*, *Fusarium solani*, *Aspergillus oryzae*, *Curvularia hawaiiensis*, *Cladosporium herbarum*, *Curvularia pallescens*, *Alternaria alternata*, *Drechslera nodulosa*, *Myrothecium verrucaria*, *Epicoccum nigrum*, *Aspergillus terreus*, *Phaeoramularia calotropidis*, and *Guignardia bidwellii*	-	Antibacterial activity	Jain et al. [143]; Katewa and Galav [153]; Meena and Rao [144]; Nascimento et al. [85]; Rani et al. [154]
	Leaves, stems and flowers		-	*Penicillium* sp. and *Aspergillus* sp.	Phenolics and Flavonoids	Antioxidant activity	Nagda et al. [155]
	Leaves and stems		-	*Myrothecium verrucaria*	-	Antitumor activity	El-Khawaga et al. [91]
Calotropis gigantea (L.) W.T. Aiton	Leaves	Helpful in easy delivery, diarehoea and malaria. Latex used in diarrhoea and burns. The milky latex is applied to remove warts and unhealthy granulations from ulcers. Bruised fresh root bark and leaves are mixed with cow urine and applied against wasp and scorpion sting.	-	*Phoma* sp.	Taxol	Anti-proliferative activity	Jain et al. [143]; Meena and Rao [144]; Singh et al. [148]; Upadhyay et al. [204]; Hemamalini et al. [86]
	Leaves and stems		-	*Phomopsis asparagi*	-	Anti-candidal	Nath and Joshi [156]
Ziziphus mauritiana Lam.	Different plant parts	Decoction of roots; stem bark powder cure from fever and also act as blood purifier.	-	*Trichoderma viride*	3-β-Hydroxy-urs-12-en-28-oic acid	Anti-cancer activity	Jain et al. [143]; Sheeba et al. [157]
Withania somnifera (L.) Dunal	Roots, stems and leaves	Provide relief from painful swellings. Bruised paste is applied locally. One tea spoon powder is taken with water once a day for 7 days	*Bacillus amyloliquefaciens* (MPE20) and *Pseudomonas fluorescens*	*Fusarium solani*, *Alternaria* sp., and *Fusarium* sp.	-	Antibacterial and immunomodulatory activity	Katewa et al. [135]; Upadhyay et al. [204]; Salini et al. [95]; Mishra et al.

Table 1 (*Continued*)

Plant	Plant parts	Ethnomedicinal uses of plants in Rajsthan	Bacteria	Fungus	Bioactive molecule	Pharmaceutical activity	References
		to cure from fever. Mature leaves smeared with butter or oil are warmed and tied locally on boils, pimples and around the neck to relieve tonsils. To stop habitual miscarriage in women a decoction of its root with black pepper and alligator pepper is an effective remedy for toning up the uterus of women. Extract of root is mixed with sugar and milk and taken as tonic in debility. Root paste is applied to carbuncles, ulcers and painful swellings.					[158]; Atri et al. [96]
	Leaves		-	*Alternaria alternata*	L-Asparaginase	Chemotherapeutic agent	Moharram et al. [94]
Moringa oleifera Lam.	Roots, stems and leaves	Leaf and fruit used arthritis, diarrhoea and vata roga. Leaves, flowers and pods are cooked as vegetable and eaten to cure rheumatism. The stem bark is rubbed on stone with water and taken orally to cure stomachache and smeared locally on swelling. The bark is boiled in water and steam is used to foment to relieve joint pain. Leaf juice with goat milk and sugar is given orally to treat dyspepsia, flatulence and colic. Leaf juice is given orally in diarrhea and cholera. Roots or leaves are crushed with lime and smeared against dog bite and snake bite. Roots and stem bark are crushed, applied locally to relieve rheumatic pain or seed oil is used to massage the body for same purpose.	-	*Colletotrichum* sp., and *Cladosporium* sp.	-	Antibacterial activity	Meena and Rao [144]; Upadhyay et al. [204]; Atri et al. [96]; Hossain et al. [186]; Salah Maamoun et al. [187]
	Barks		-	*Aspergillus fumigatus*	Caffeic acid, Rutin, Ellagic acid, Quercetin, and Kaempferol	Antibiofilm, antiproliferative, antioxidant, and antimutagenic activities	[159,81]
Salvadora oleoides Decne.	Roots, stems and leaves	The oil extracted from seeds is applied in rheumatic pain. Decoction of unripe fruits is given to cure enlarged spleen and rheumatic fever. Stem bark is soaked in whey with the bark of *Capparis decidua* in a brass pot to which a copper coin is added and kept overnight. Leaves are used in dry cough and fruits are useful in asthma and digestive disorders.	*Pseudomonas*	*Aspergillus* sp., *Epicoccum nigrum*, *Neosartorya glabra*, and *Phoma* sp.	Tannin, Terpenoid, Alkaloids, Phenols, and Saponin	Antimicrobial activity, hypoglycaemic and hypolipidemic activities, and antibacterial activity	Upadhyay et al. [204]; Korejo et al. [119]; Saket and Arnold [118]
Salvadora persica L.	Roots, stems and leaves	Fruits are employed in calculi, constipation, indigestion and stomatitis. Seed oil applied in rheumatic pain. Gadulia lohar tribe takes root decoction orally to cure fever. Constipation paste of 8–10 crushed leaves is taken orally with water. Blisters paste is applied locally.	*Pseudomonas*	-	-	Antibacterial activity	Katewa et al. [135]; Katewa and Galav [153]; Korejo et al. [119]
Prosopis juliflora (Sw.) DC	Leaves	_	*Bacillus*, *Staphylococcus*, and *Aerococcus*	*Colletotrichum gloeosporioides*	-	Antimicrobial activity	Khan et al. [98]; Srivastava and Anandrao [160]

Table 1 (*Continued*)

Plant	Plant parts	Ethnomedicinal uses of plants in Rajsthan	Bacteria	Fungus	Bioactive molecule	Pharmaceutical activity	References
Euphorbia hirta L.	Roots, stems and leaves	Plant paste is taken with water to cure dysentery. Plant extract is also given orally to children to febrifuge. Juice of whole plant is used in diarrehea. Latex is applied on pimples to cure from pimples. Decoction of whole plant, latex asthma, bronchial infection, typhoid, pneumonia, dysentery, colic pains, eczema, etc. 10–20 g leaves are crushed into paste, mixed in whey and given orally in diarrhea. The fresh latex is applied to warts and the treatment needs to be repeated 2–3 times a day. Plant extract is mixed with 2 kg boiled gram pulse and equal amount of honey and taken by women to cure leucorrhoea. Whole plant is decocted and taken internally and paste is also applied on affected area in the treatment of athlete's foot.	*Actinomycetes* strain EHL27	*Achaetomium* sp.	Phenols, Flavonoids, and Tannins	Hepatoprotective, antimicrobial, and antioxidant activities	Jain et al. [143]; Jain et al. [136]; Upadhyay et al. [204]; Meena and Yadav [161]; Syed et al. [162]; Anitha and Mythili [163]
Aloe vera (L.) Burm.f.	Leaves gel	Leaf cut laterally, and *Curcuma aromatica* poweder is sprinkled on the cut portion, warm and tied locally on both sides of fracture bone. After 3-4 hrs the bone is then set in correct position and plastered. Fresh leaf pulp is tied as bandage on deep cut for early healing. Indigestion two hundred and fifty grams of fresh pulp along with a pinch of black pepper and black salt is taken empty stomach for 7 days.	*Bacillus cereus*, *B. licheniformis. Lactobacillus paralimentarium*, and *Clavispora lusitaniae*	*Chaetomium globosum*, *Trichoderma harzanium*, and *Preussia africana*	Butyrate	Anti-inflammatory activity and anticancer activity	Katewa et al. [135]; Jain et al. [136]; Meena and Yadav [161]; Al-Madboly et al. [104]; Chowdhary and Sharma [105]; Ameen et al. [164]
Acacia nilotica L.	Leaves	Leaf, stem powder in toothache. Root decoction is mixed with sugar candy, cardamom, and *Asparagus* and taken by females against body heat for 15 days. The pod paste mixed with candy is taken empty stomach in the morning by female, to treat leucorrhoea completely. Seeds are ground with sugar candy and eaten daily for 3 days by females for conception. The bark is crushed with that of *Azadiracta*, mixed with lemon juice and applied as an ointment against ringworm for 5 days.	-	*Aspergillus awamori*	Peptide with alpha glycosidase inhibitory activity	Antidiabetic activity	Upadhyay et al. [204]; Sharma and Kumar [165]; Singh and Kaur [166]
Chenopodium album L.	Leaves	Cooked leaves as a vegetable given in urinary trouble. A tea of the leaves and plant is used to relieve stomach pains. Decoction of seeds is given as a drink to women during labour pain for early and easy delivery.	-	*Stemphylium botryosum*	Dehydrocurvularin, Altersolanol, Tetrahydroaltersolanol, Stemphyperylenol, Macrosporin, and Curvularin	Cytotoxic activity	Aly et al. [167]; Sharma and Khandelwal [168]; Upadhyay et al. [204]
Bacopa monnieri L.	Leaves and branches	To Cure Cough. Warmed leaf paste helpful in abdominal ache, urinary, etc.	-	*Fusarium oxysporum* and *Fomitopsis* sp.	-	Cytotoxic and antimicrobial activity	Jain et al. [143]; Singh et al. [148]; Katoch et al. [169]
	-		-	*Aspergillus* sp.	Bacopaside		Jasim et al. [170]
Ephedra foliata Boiss. ex C. A. Mey	Stems	_	*Paenibacillus* and *Microbacterium Kytococcus*	-	-	Anti-bacterial, anti-oxidant, and anti-cancer properties	Ghiasvand et al. [129]
Tribulus terrestris L.	Leaves	Fruit powder with *Sesamum indicum* (til) seeds are taken	-	*Curvularia aeria*	-	Antioxidant activity	Jain et al. [143]; Katewa and

Table 1 (*Continued*)

Plant	Plant parts	Ethnomedicinal uses of plants in Rajsthan	Bacteria	Fungus	Bioactive molecule	Pharmaceutical activity	References
		orally by the rural men to cure impotency. Fruit powder is given orally to cure urinary disorders and mixed with sugar is given for easy delivery. Fruit powder also useful in renal disorder and leucorrhoea.					Galav [153]; Sahani et al. [171]
Datura metel L.	-	Cure insunity, cerebral complication. Sahariya and Bhil tribe used Inflorescence and seeds to cure from cough, gonorrhea, antihelmintic, wounds, leprosy.	*Stenotrophomonas* sp. and *Pseudomonas* sp.	*Bipolaris* sp. and *Fusarium solani*	Ophiobolin-	Anticancer activity and cytotoxic activity	Jain et al. [143]; Sharma and Kumar [165]; Kuriakose et al. [121]; Rania et al. [123]; Maehara et al. [124]
Datura stramonium L.	Stems, leaves, flowers and seeds		*Stenotrophomonas maltophilia* str. S37 and *Bacillus mojavensis* str. S40	*Alternaria* sp.	Anserinone B and Phelligridin B	Cytotoxic activity	Ben Abdallah et al. [125]; Tapfuma et al. [126]

and root samples of both *S. persica* and *S. oleoides* [119] Young and old stem and 125 root segments were processed for the isolation of endophytes and resulted in forty-two fungal isolates namely, *Trichoderma*sp., 2 species of *Alternaria*, *Rhizopus arrhizus* and 6 sterile mycelia [120].

7.6. Endomicrobial diversity of Datura spp.

Datura metel L. and *D. stramonium* L. belonging to the family Solanaceae are the important medicinal plants traditionally used as a remedy for several diseases like narcotic, aphrodisiac, febrifuge, anthelmintic, topically applied to remove tumors [121], stimulation of the central nervous system, respiratory decongestion, treatment of dental and skin infections, alopecia, and the treatment of toothache [122]. Their broad spectrums of therapeutic activities are attributed to tropane alkaloids, atropine, and scopolamine obtained from its plant parts. Thus, it is widely harnessed by the pharmaceutical industries. Two bacterial endophytes *Stenotrophomonas* sp. str. S33 and *Pseudomonas* sp. str. S85 [123] and two fungal endophytes filamentous fungus *Bipolaris* sp. [124] and *F. solani* strain [121] were recorded from stems, leaves, flowers, fruits, and roots samples of *D. metel* L.

Ben Abdallah et al. [125] demonstrated that ten bacterial endophytes have been isolated from the healthy plant tissues of *D. stramonium*. Tapfuma et al. [126] isolated eleven endophytic fungi from the aboveground plant parts of *D. stramonium.* The isolation of endophytic fungi leads to the isolation of bioactive molecule i.e. anserinone B, phelligridin B from the crude extract of *Alternaria* sp. KTDL7 with potent cytotoxic activity on UMG87 glioblastoma cells (IC_{50} = 21.49 μg/ml) [126]. Furthermore, an endophytic fungus *Colletotrichum incarnatum* species belongs to class Sordariomycetes of phylum Sordariomycete, has been reported from the leaf of *D. metel* identified on the basis of morphological as well as ITS sequencing [127].

7.7. Endomicrobial diversity of Ephedra foliata

Ephedra foliata belongs to the Ephedraceae family, is a well-known source for the alkaloid, ephedrine. Ephedrine is used for the treatment of chronic asthma and associated respiratory ailments from ancient times [128]. Bacterial endophytes belonging to 10 different taxa were isolated from the healthy stem of *E. foliata* related to *Firmicutes*, *Actinobacteria*, and *Proteobacteria.* Isolated bacterial endophytes were five strains from *Bacillus*, two strains from *Paenibacillus*, and one strain from *Brevundimonas*, *Kytococcus*, and *Microbacterium* [129].

7.8. Endomicrobial diversity of Moringa oleifera

A traditional ethnomedicinal plant *M. oleifera* belongs to the family Moringaceae, possess nutritional and medicinal properties due to the presence of naturally derived bioactive molecule. *M. oleifera*, a native plant to India, grows well in hot, humid, and dry climatic conditions, therefore, it is found throughout the world [130]. It is known as horseradish tree or drumstick tree and has been widely used as antimicrobial, hepatoprotactive, antidiabetic, and antitumor agent [193]. Abonyi et al. [131] isolated an endophytic fungus *Aspergillus* sp. from the leaf tissues of *M. oleifera* with potential antimicrobial and antioxidant compounds such as p-hydroxyphenyl acetic acid and ferulic acid. In addition to this, an endophytic fungus *C. globosum* also reported from *M. oleifera* with good antimicrobial activity against some resistant clinical isolates [132]. Atri et al. [96] reported a total of twenty-one endophytes in their study among them four potent isolates were identified as *Colletotrichum* sp., *Cladosporium* sp., and *Fusarium* sp. Moreover, Mwanga et al. [133] have isolated two fungal endophytes namely *Nigrospora* sp. from leaf tissues and *Fusarium* sp. from roots and seeds of *M. oleifera*. Aldinary et al. [134] reported three fungal endophytes from the leaf tissues of *M. oleifera* identified as *Aspergillus alabamensis*, *Aspergillus tubingensis*, and *Aspergillus oryzae* [134]. Table 1 shows endophytic microflora of ethnomedicinal plants of the Thar Desert and their biopotential applications.

8. Biopotential of isolated fungal endophytes from Thar Desert plants

Medicinal plants have been using as indispensable resources of medicine since time immemorial. In developing countries like India, almost 80% of folks use remedies derived from medicinal plants to cure their ailments. Medicinal plants are identified as a rich source of naturally derived secondary metabolites to cure diseases aliments [172]. Therefore, the presence of endophytic microflora seems to be beneficial to their host since the production of secondary metabolites is owed to these residing endophytic communities. These bioactive molecules enhanced not only the fitness of the host by means of increased resistances against parasitism, herbivore, and drought condition but also their growth too. A variety of bioactive molecules have been produced by endophytes such as xanthones, tetralones, benzopyranones, alkaloids, flavonoids, terpenoids quinones, phenolic acids, and chinones and such bioactive metabolites find wide-ranging use as agrochemicals, antiparasitics, antibiotics, antioxidants, and anti-cancer agents [6]. Table 2 shows the chemical structure representation of various bioactive molecules isolated from endophytic communities of medicinal plants of the Thar Desert. Nearly 8000 various kinds of medicinal plants have been reported for their use in medicines, biocidal products, dietary supplements, and other phytochemicals. These secondary metabolites derived from endophytic microflora possess various kinds of natural properties such as antimicrobial, antibiotic, anticancerous, antidiabetic, antioxidant, and anti-inflammatory activities [172] (Fig. 3). According to previous studies, biopotential endophytic microflora of the medicinal plants of the desert reveals that they also possess some kind of therapeutic activities, since they play a crucial role in the synthesis of bioactive molecules in the host plant.

Endophytes are highly diverse polyphyletic domains and their diversity has a profound effect on the production of secondary metabolites. Therefore, this rationale has lead to the discovery of potential endophytes from medicinal plants. On the basis of the literature survey, it has been evidenced that secondary metabolites obtained from medicinal plants and their endophytes impart to a major percentage of naturally derived drugs in the market (202,198). Varieties of such bioactive molecules with therapeutic value have been identified to date, for example, paclitaxel (also known as Taxol), camptothecin, azadirachtin, deoxypodophyllotoxin, and podophyllotoxin [70]. The secondary metabolites synthesized by endophytes not only have ecological importance but also support a scientific handle to investigate the biochemical and molecular frameworks associated with their synthesis [173].

9. Antimicrobial activity

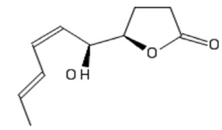
Several phytochemical showing antimicrobial potential against recently emerged drug-resistant human pathogens, have been obtained from the endophytic microflora. These bioactive molecules from medicinal plants are proving to be more effective, have low toxicity, and have a low environmental impact [174,188]. A total of six fungal isolates from leaf samples of *C. procera* have been shown strong antibacterial activity against human pathogenic microbes' *viz.* Gram-positive bacteria, *Staphylococcus aureus*, *Streptococcus pyogenes*, alcohol-acid resistant bacteria [85] *Bacillus subtilis*, *Klebsiella pneumoniae*, *S. epidermidis*, and *E. coli* [192]. The endophytic fungi *Curvularia pallescens*, *C. cladosporioides*, *Xylaria* sp., morphotaxa 2 and 3, and hyphomycetes 2 have known to displayed antimicrobial activity due to the production of several secondary metabolites. The fungal endophytes from leaves of *C. procera* have depicted huge pharmacological potential against Gram-positive and alcohol-acid resistant bacteria [85]. Some endophytic fungus also exhibits anti-candidal activity against *C. albicans*. A fungal isolate *Phomopsis asparagi* from *C. gigantea* was evaluated for *in vitro* and *in vivo* anti-candidal potential against *C. albicans. Phomopsis asparagi* showed intense *in vitro* anti-candidal activity with a minimum inhibitory concentration (MIC) of 46.9 μg/mL. Different organs of mice were studied for any deformities during the evaluation of *in vivo* anti-candidal activity on mice and reflected *C. albicans* displayed many cell deformities when treated with the *P. asparagi.* Hence, *P. asparagi* can be a potential source for anti-candidal compounds for *C. albicans* [156].

Out of the total 20 fungal endophytes from *C. procera*, seven endophytic fungal crude ethyl acetate extracts displayed antibacterial activity against all tested bacterial strains using agar well diffusion assay. *Aspergillus nomius*, *F. solani*, *Aspergillus oryzae*, and *Curvularia hawaiiensis* displayed significant antibacterial activity against *S. typhi*, *S. flexneri*, *S. typhi* and *S. marcescens*, respectively. Apart from the above-mentioned endophytes, *Aspergillus nidulans*, *Chaetomium arcuatum*, and *Chaetomium atrobrunneum* displayed the best antibacterial activity against all tested bacterial strains. The endophytic fungi belonging to the genus *Aspergillus* and *Fusarium* demonstrated good antibacterial activity with a minimum inhibitory concentration (MIC) of 15.6 μg/well to 250 μg/well. This study reflected that fungal extracts of endophytic isolates were more efficient against Gram-positive bacteria than Gram-negative [154,175]. Eighteen endophytic fungal isolates were obtained from roots of *C. procera*, among them, only one endophytic fungus has been *Aspergillus niger* identified to show strong antimicrobial activity against Gram-positive, Gram-negative bacteria, and fungi.

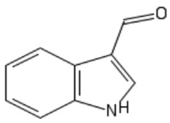
The antimicrobial activity was assessed against *Escherichia coli*, *Pseudomonas aeroginosa*, *B. subtilis*, *S. aureus*, *Ralstonia solanacearum*, *Xanthomonas oryzae*, *P. chrysogenum*, *C. albicans*, *Phoma exigua*, *Sclerotium rolfsii*, and *Sclerotinia scleratiourum* by employing the disc diffusion method [35–37]. Actinomycins displayed a wide-array of antimicrobial activity towards multidrug-resistant Gram-positive and Gram-negative bacteria and fungi. A bacterial endophyte *Streptomyces parvulus* NBRC 13193T associated with root tissues of *Aloe vera* has been characterized for the production of actinomycin D and actinomycin X0β (400 mg/L) by the fermentation of glucose soybean meal broth media [176]. The antimicrobial potential of endophytic isolates can alter not only by the age and development stage of the leaf samples to be processed but also by culture media too. A total of 148 endophytic fungi were recovered from the leaf tissues of different ages of *Ocimum sanctum* Linn. of which 134 isolates showed antimicrobial activity against at least one test microorganisms.

The study reflected that fungal crude ethyl acetate extract of fungal isolates from the healthy leaves at older stages cultured on yeast extract sucrose broth showed best antimicrobial activity than others cultured on malt extract broth [177]. A fungal isolate, *Lasiodiplodia pseudotheobromae* from the leaf of *Ocimum sanctum* Linn. were subjected for antibacterial activity against both Gram-positive (*S. aureus* [MRSA] ATCC 33591, *S. aureus*, *Streptococcus mutans*, *Bacillus cereus* ATCC 10876, *B. subtilis* IBRL A3, *and Streptococcus agalactiae*) and Gram-negative (*K. pneumoniae* ATCC 13883, *Salmonella typhimurium*, *Shigella boydii* ATCC 9207, *Escherichia coli* IBRL 0157, *Proteus mirabilis*, and *Pseudomonas aeruginosa* ATCC 27883) bacteria using an agar plug assay. Results revealed that the fungal isolate displayed antibacterial activity against all the test bacteria. Quantitative assessment of antimicrobial activity of fungal crude extract by using disc diffusion assay depicted that the fungal ethyl acetate extract prepared from the extracellular fungal material displayed best antibacterial activity than methanolic extract prepared from the intracellular fungal biomass [111]. Cell-free culture of endophytes also exhibited strong antibacterial activity towards human pathogenic bacteria. A total of 35 endophytic isolates of fluorescent *Pseudomonas* have been recorded from leaf, shoot and root tissues of *S. persica* and *S. oleoides.* Isolates showed antibacterial activity against Gram-negative (*Escherichia coli*, and *Salmonella typhimurium*) and Gram-positive (*B. subtilis* and *S. aureus*) bacteria [119]. Ethyl acetate extract of six fungal endophytes (*Fusarium semitectum*, *Fusarium avenaceum*, *Fusarium* sp., *F. oxysporum*, *Aspergillus* sp., and *Fusarium redolens)* isolated from *W. somnifera* displayed better antimicrobial activity against *B. subtilis*, *S. aureus*, *E. coli*, and *K. pneumoniae*. Among them, ethyl acetate extract of *Fusarium* sp. and

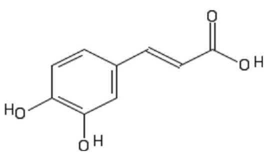
Table 2
Chemical structures of bioactive molecules isolated from endophytic communities of medicinal plants of the Thar Desert.



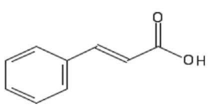
Sapinofuranone B



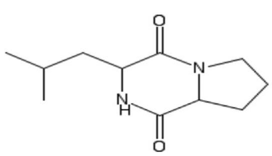
3-Indolealdyhide



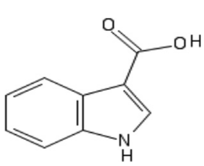
Cafeic acid



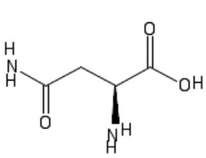
Cinnamic acid



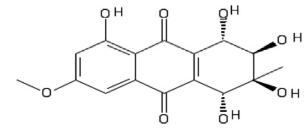
Cyclo (leu-pro)



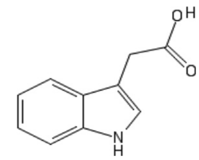
Indole-3-carboxylic acid (ICA)



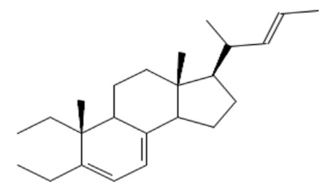
L-Asparginase



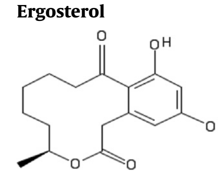
Altersolanol



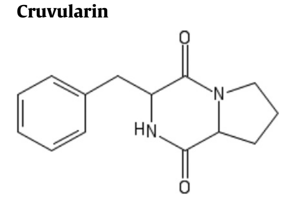
Indole-3-acetic acid



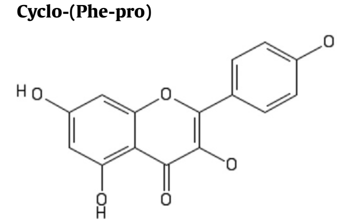
Ergosterol



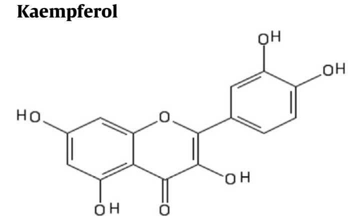
Cruvularin



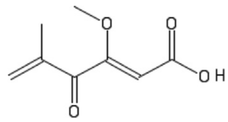
Cyclo-(Phe-pro)



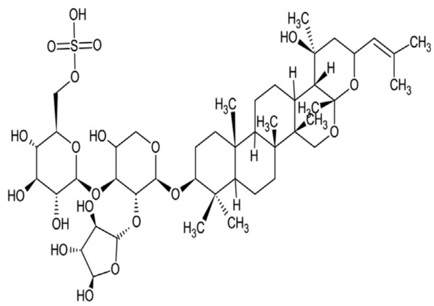
Kaempferol



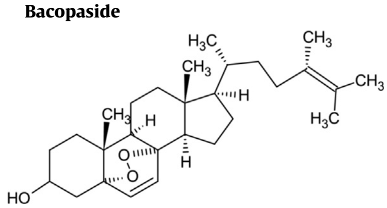
Quercetin



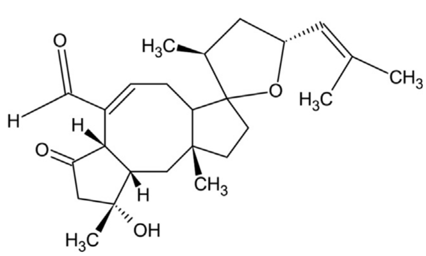
Penecillic acid



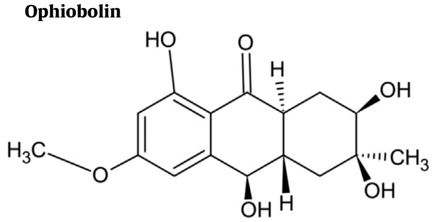
Bacopaside



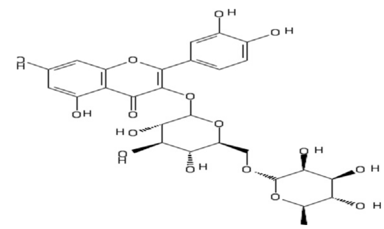
Ergosterol-peroxide



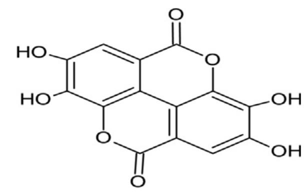
Ophiobolin



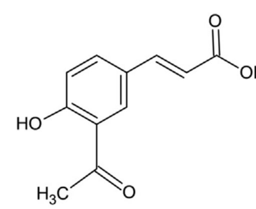
Tetrahydroaltersolanol B



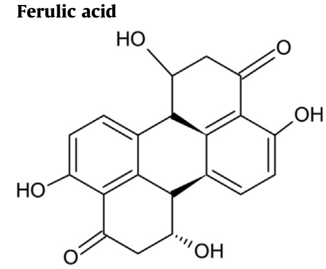
Rutin structure



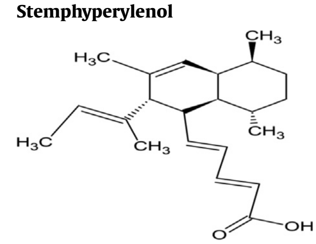
Ellagic acid



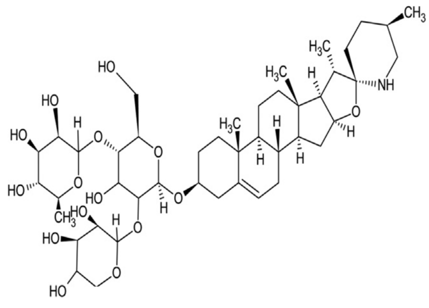
Ferulic acid



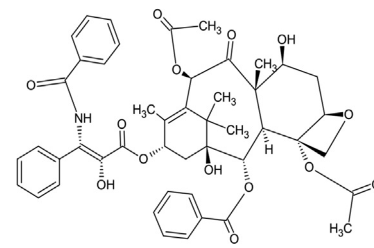
Stemphyperylenol



Phomopsidin



Solamargine



Taxol

Aspergillus sp. displayed maximum activity against *S. aureus*, *E. coli*, and *B. subtilis* [95]. A Gram-negative bacteria strain of *Escherichia coli* and a Gram-positive strain of *S. aureus* were proved to be susceptible to 24 fungal endophytic strains isolated from *M. oleifera* and *W. somnifera*. The study reflected that four active isolates from *M. oleifera* namely, *Colletotrichum* sp., *Cladosporium* sp., and *Fusarium* sp., and two active isolates from *W. somnifera* namely, *Alternaria* sp., and *Fusarium* sp. had antagonistic activity towards both the bacterial strains [96]. Eight fungal endophytes isolated from *Solanum mauritianum* exhibit antituberculosis activity towards *Mycobacterium tuberculosis*.

Fungal isolates were recorded from leaves and unripe fruit of *Solanum mauritianum* and identified as *Aureobasidium pullulans*, *Paracamarosporium leucadendri*, *Cladosporium*sp., *Collectotrichum boninense*, *Fusarium*sp., *Hyalodendriella*sp., and *Talaromyces*sp., and *P. chrysogenum*. Apart from *Mycobacterium tuberculosis* some other pathogenic bacteria also prove to be susceptible to endophytic isolates. Among all the isolates, *Paracamarosporium leucadendri* and *Fusarium*sp. showed maximum antimicrobial activity against *Mycobacterium bovis*, *K. pneumoniae*, *P. aeruginosa* and *Mycobacterium smegmatis* [100]. Another species of *Solanum*, *S. surattense* also harbor some endophytic fungi with antimicrobial and antioxidant potentials. Two out of four fungal isolates from the root tissues of *S. surattense*, *P. roqueforti* and *T. reesei* showed antibacterial activity [101]. Bacterial endophytic belonging to 10 different taxa were recorded from healthy *E. foliata* out of which two strains of Paenibacillus depicted adequate antibacterial activity towards *S. aureus*, *B. subtilis*, *P. aeruginosa*, and *Escherichia coli*. Biochemical characterization of isolates revealed the presence of plant-related bioactive compounds such as alkaloid, aminoglycoside, flavonoid, and terpenoid [129].

10. Anticancer activity

Endophytic microflora from medicinal plants shows broad-spectral anticancer bioactivities. Bacterial endophytic belonging to 10 different taxa were recorded from healthy *E. foliata* out of which *Kytococcus* showed the highest cytotoxic activity on HeLa cancerous cell. The anticancer properties of *Kytococcus* were examined by the extraction of the fungal crude extract by chloroform with IC_{50} values (μg/ml) 104, 64, and 43 after 24, 48, and 72 hours, respectively [129]. Strong anti-proliferative activity of a taxol producing endophytic fungus *Phoma* sp. isolated from *C. gigantea*, against MCF-7 cell lines was observed *in vitro*. The presence of taxol in the fungal crude extract was characterized by using chromatographic and spectroscopic approaches regarding commercial taxol. Quantitative assessment of the amount of taxol produced by the *Phoma* sp. was revealed, which is 76.13 μg [86]. A

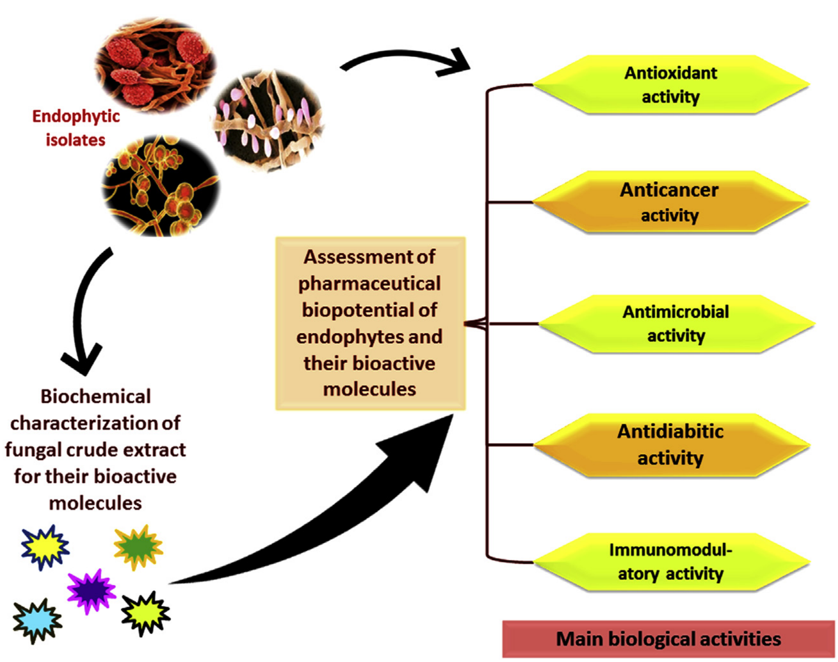


Fig. 3. Isolation and characterization of bioactive molecules from endophytes reported from ethnomedicinal plants and their areas of application.

chemotherapeutic agent, L-asparaginase enzyme employed for the treatment of cancer and tumor diseases. A plethora of microbial sources have been subjected to the production of L-Asparaginase. For example seven endophytic fungi *viz. A. alternata*, *Aspergillus aculeatus*, *C. globosum*, *Cladosporium cladosporioides*, *Eurotium rubrum*, *Petromyces flavus*, *Pleospora allii*, and two sterlia mycelia (Dark sterile mycelium and white sterile mycelium) reported from leaf samples of *W. somnifera.*

All isolated endophytic fungi can produce L-asparaginase enzyme except *Eurotium rubrum* within the range of 1.1 ± 0.03 – 1.98 ± 0.16 IU [94]. The ethyl acetate (EtOAc) extract of an endophytic fungal strain *F. solani* isolated from *D. metel* L., were tested for its anticancer properties on distinct cancer cell lines by MTT assay. Results reflected that EtOAc extract of *F. solani* displayed strong anticancer properties towards all the tested human cancer cell lines, specifically towards cervical cancer HeLa cells by means of induction of cell apoptosis through the mitochondrial pathway, disruption of mitochondrial membrane potential, DNA fragmentation and nuclear chromatin condensation [121,178]. Remarkable cytotoxicity was reported from the crude ethyl acetate extract of *Alternaria* sp. KTDL7 endophytic fungi out of eleven endophytic fungi were recovered from stems and leaf samples of *D. stramonium*, on UMG87 glioblastoma cells with IC_{50} value is 21.49 μg/ml.

Biochemical characterization of crude ethyl acetate extract of *Alternaria* sp. by using LC-QTOF-MS/MS demonstrated the presence of some bioactive molecules, documented as cytotoxic in the literature *viz.* anserinone B and phelligridin B [126]. Fungal crude extracts an endophytic fungus *Myrothecium verrucaria* isolated from leaf and stem samples of *C. procera* identified to possess antitumor activity similar to vinblastine sulphate as reference drug against colon cancer cell line, liver cancer cell line, and breast cancer cell line [91]. An endophytic fungus *Aspergillus* sp. isolated from *Aloe vera* synthesize amylase enzyme which depicted mild antiproliferative activity against MOLT-3 cell line [179].

11. Antioxidant activity

Bacterial endophytic belonging to 10 different taxa were recorded from healthy *E. foliata* out of which fungal crude extract of *Microbacterium* by chloroform displayed good antioxidant activity with strong DPPH scavenging capacity (EC_{50} at 43.0 μg/ml) [129]. Two endophytic fungi *Penicillium* spp. and *Aspergillus* spp. isolated from *C. procera* identified to possess antioxidant activity. Phytochemical screening of fungal crude methanolic extracts of *Penicillium* spp. and *Aspergillus* spp. revealed the number of phenolics and flavonoids present in the extracts. So, it has been suggested that the antioxidant activity of endophytic fungi would be attributed to the flavonoids and phenolics compounds present in the crude methanolic extracts [155]. A total of four endophytic fungi *viz. Myrothecium verrucaria*, *A. alternata*, *E. nigrum*, and *A. terreus* were discovered from leaf and stem samples of *C. procera.* All fungal isolates displayed good antioxidant activity at 5 μg/ml [91]. A fungal endophyte belonging *Nigrospora* genus isolated from the leaf sample of *O. basilicum* var. *thyrsiflora* displayed high antioxidant activity with IC_{50} value of 15.36 mg/mL. The antioxidant property of fungal crude extracts was examined by DPPH radical scavenging assay.

The presence of six major compounds responsible for antioxidant activity of extract comprising farnesyl acetone, columellarin, totarene, laurenan-2-one, and 8S,13-cedranediol into fungal crude extracts, were identified by using GC–MS [110]. Endophytic fungi isolated from the root tissue of *Ocimum sanctum* Linn. identified for their antioxidant activities. Crude ethyl acetate extract of TRF-1 and TRF-2 were investigated for free radical scavenging properties towards 2,2-diphenyl-1-picrylhydrazyl, hydroxyl free radicals, and reducing power assay. TRF-1 was observed to a potential source of antioxidant activity with IC_{50} values of 71.83 μg/ml for DPPH and 110.85 μg/ml for hydroxyl radical, respectively. Fungal isolate TRF-1 was identified as *Paecilomyces variotti* by using morphological structure and molecular characterization [112]. Characterization of biochemical compounds purified from an endophytic fungus *Curvularia aeria*, recorded from leaf tissues of *Tribulus terrestris*, revealed the presence of phenol, flavonoids, terpenoids, steroids, alkaloids, etc., in distinct solvents extracts.

Further, extract of *Curvularia aeria* examined for its antioxidant properties based on scavenging of free radicals such as ABTS, DPPH, hydrogen peroxide, hydroxyl radical, metal cheating, nitric oxide, superoxide radical, reducing power and FRAP methods, and reflected its strong antioxidant activity [171]. An experimental study on ethyl acetate extract of endophytic fungus *Achaetomium* sp., recorded from *E. hirta* suggests that it demonstrates antioxidant potential due to the presence of phenolic, flavonoid, and tannin content. It was examined by using DPPH radical scavenging assay and well diffusion assay and revealed the amount of present phenolic content (44.02 ± 1.57 mg), flavonoid content (54.54 ± 1.82 mg), and tannin content (18.790 ± 1.018 mg) [163].

12. Immunosuppressive compound

Fungal crude ethyl acetate extract of endophytic fungi isolated from the root tissue of *Ocimum sanctum* Linn. TRF-3 and TRF-6 exhibited immunomodulatory activities *in vitro* by chemotaxis assay. TRF-3 and TRF-6 exhibit the maximum number of neutrophils at 100 μg/mL which was comparable with the standard. These results reflected the immunostimulatory activity of endophytic fungi from *Ocimum sanctum* [180]. Six endophytic fungi isolated from root tissues of *W. somnifera* displayed better immunomodulatory potential with increasing phagocytic activity. Among all fungal isolates, *F. solani* and *Aspergillus* sp. exhibit more phagocytic activity than other isolates. Pheno l,2,4-bis(1,1-dimethyl ethyl), benzene propanoic acid, 3,5-bis(1,1-dimethyl), and carnegine have been identified as pharmaceutically important bioactive molecule present in the fungal crude ethyl acetate extract based on GC-MS analysis [95].

13. Antidiabitic activity

The development of anti-diabetic drugs from endophytes would be a better approach than synthetic drugs due to their rapid growth rate, lesser space required for the culture growth, and easy extraction method. Therefore, purified bioactive molecules from endophytes have the potential to rise as a prominent natural compound that can cure diabetes. A compound that showed inhibitory action against α-glucosidase enzyme was purified from an endophytic fungus *Alternaria destruens* dwell inside healthy tissues of *C. gigantea*. The study suggested that the fungal isolate may be the promising source of the novel drug to cure diabetes [159,181]. Thirty six endophytic fungi recovered from healthy stem and leaf tissues of *A. nilotica* were examined for the production of inhibitors against alpha-amylase and glucosidase. The study revealed that crude extract of *Aspergillus awamori* displayed inhibitory activity towards both enzymes alpha-amylase and glucosidase. The inhibitory activity of the extract is attributed to a proteinaceous compound present in it. Identified inhibitory compounds showed mixed types of inhibition with IC_{50} values of 3.75 and 5.625 μg/ml against alpha-amylase and alpha-glucosidase, respectively [166]. It has been studied that some endophytic fungi isolated from *Ocimum sanctum* produce bioactive molecules with anti-diabetic properties independently without plant components in them. Hence, proving to be the most useful approach as anti-diabetic agents without destroying medicinal plants. Characterization of crude ethyl acetate extracts of four endophytic fungi *Alternaria tenuissima*, *Colletotricum gloesporioides*, *Diaporthe* sp. and *Trichoderma* sp., isolated from *Ocimum sanctum* showed their IC_{50} values fall into proximity of IC_{50} values of acarbose and quercetin standard [49,50,182].

14. Antibiofilm Activity

Secondary metabolites obtained from chloroformic fungal extract of *Aspergillus fumigatus*, an endophytic fungus reported from *M. oleifera* demonstrated an effective antibiofilm activity towards several pathogenic microbes [159,181]. Singh and Dubey [183] reported potent antibiofilm activity of secondary metabolites isolated from the crude extract of a novel strain of endophytic actinobacterium i.e. *Streptomyces californicus* strain ADR1 recovered from the *D. metel*, against the strain of *S. aureus* [183].

15. Conclusion

In the context of the current scenario, there is an urgent need of finding naturally derived secondary metabolites for the treatment of various diseases. Endophyte has been identified as a vital source of production of secondary metabolites and the model to identify the biosynthetic pathway of those naturally derived molecules. According to the previously mentioned studies, endophytes play a crucial role in the synthesis of pharmaceutically important compounds similar to their host. However, the production of the useful naturally derived compound at the commercial level still has to achieve. In this review, we have tried to shed light on desert plant-fungal endophytes interaction. The arid ecosystem of the Thar Desert of Rajasthan is known as a rich repository of ethnomedicinal plants that used not only as a herbal drug but also as a potential source of gum, resin, essential oils, tannin, etc. Pieces of literature reported that a plethora of pharmaceutically important compounds have been isolated from the ethnomedicinal plants of the Thar Desert such as alkaloids, peptides, flavonoids, phenolics, taxol, camptothecin, etc. The development of resistance in human pathogenic microorganisms against antibiotics has become a big problem before the researchers thus there is a huge requirement for the discovery of novel and naturally derived drug molecules. Endophytic fungi showed a variety of properties like antibacterial, antidiabetic, anticancer, antitumor, antifungal, antimalarial, antioxidant, antiviral, and immunomodulatory activities, thus endophytic microflora can serve as a good alternative source for pharmaceutically important compounds. These studies about the role of endophytes in the synthesis of bioactive molecules lay the foundation for further research directed to the studies scale-up their production. In the future, an attempt to have an advanced molecular level and genetic levels research to identify the regulatory gene of the biosynthetic pathway of metabolite construction may scale up the production of endophytic microflora-derived pharmaceutically important compounds and also improve our insight into endophytic biodiversity for human welfare.

Author's contributions

MM and GY conceived the idea of the review, provided the general concept and inputs for each specific section, and drafted part of the manuscript. MM and GY wrote the review after collecting literature. MM edited, compiled, and finalized the draft. Finally, all the authors read and approved it for publication.

Funding

There is no funding agency available present time.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

The author, MM is thankful to Mohanlal Sukhadia University, Udaipur for providing the necessary facilities during the course of study.

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