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Therapeutic potential of endophytic bacteria from ethnomedicinal plants used by the traditional healers of North East India

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North East Indian Himalayan Region (NEIHR) is endowed with a diverse ecosystem. The indigenous people of this region have good traditional knowledge to combat various diseases and physical ailments using ethnomedicinal plants that were gained through experience over years. Some of the plants have been incorporated in the conventional medicines. However, many of the plants have not been scientifically explored since they remain endemic to a particular region and the traditional healers kept it as secret knowledge. The majority of the endophyte of NEIHR belongs to genus *Acinetobacter*, *Bacillus*, *Microbacterium*, *Pseudomonas*, *Serratia*, and *Streptomyces*. Endophytic bacteria exhibit antimicrobial activities against important human pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella enterica*, *Streptococcus pyogenes*, *Staphylococcus aureus*, etc. Bioactive strains display potential anticancer and antioxidant activities. This review also incorporates some of the potential unexplored medicinal plants used by the ethnic population of this region for treating common diseases and the importance of exploring bioactive compounds from the associated bacteria. It will also highlight the prospects of discovering novel bioactive compounds that will have a new and novel mechanism of actions for combating the drug resistant pathogens.

Keywords: Anticancer agents, Antimicrobial, Antioxidant, Endophytic bacteria, Ethnomedicinal plants, North East India

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North East Indian Himalayan Region (NEIHR) comprises of eight states- Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim, and Tripura. The region is located between 87°32’E to 97°52’E latitude and 21°34’N to 29°50’N latitude. The region has different landscape the Eastern Himalayan, Northeast hills (Patkai Naga Hills and Lushai Hills) as well as valley and plains of Brahmaputra and Barak rivers. The region which falls under two mega-biodiversity hotspots – the Eastern Himalaya and the Indo-Burma, is endowed with diverse ecosystems[1]. The region is inhabited by around 475 diverse ethnic groups, speaking almost 400 ethnic dialects[2].

Human exploitation of plants as the major source of bioactive metabolites as therapeutic agents in combating various diseases is as old as human civilization and the search for bioactivity is still continuing since, as it has a great potential for discovery of novel health beneficial metabolites. Over 1 million natural compounds have been identified, among which 5% is derived from microorganisms[3]. The study of endophytic microbes has become an emerging field in search of discovering novel bioactive compounds for therapeutic application. Bioactive compounds extracted from microorganisms are the major sources that have been persistently used as antimicrobial agents until today[4,5]. Endophytic bacteria may be directly or indirectly involved in the production of bioactive phytochemicals. A number of endophytes have been reported to produce the same bioactive phytochemicals as host plants[6].

The ethnic people of NEIHR have rich traditional knowledge of the medicinal value of indigenous flora. The traditional knowledge on the use of

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ethnomedicinal plants in combating various diseases or physical ailments has been practiced by indigenous tribal people since time immemorial. Medicinal plants with ethnomedicinal history from this region are in folklore medicine for the treatment of various diseases or ailments such as cough, fever, gastrointestinal infection, diabetes, hypertension, cancer, malaria, ulcer, tuberculosis, urinary disorder, etc. Ethnomedicinal plants with their local name used by the ethnic people of NEIHR and their medicinal usage are given in Table 1. The people in this region are well aware of the medicinal properties of the plants in combating common diseases that was gained through experience from trial and error. The information was

Table 1 — Ethnomedicinal plants of NEIHR and parts used for isolation of endophytic bacteria

Ethnomedicinal plants	Local name	Collection site(s), State	Parts used for isolation of endophytes	Ethnomedicinal usage	Reference
Achyranthes aspera L.	Khujumpere	Manipur	Stem, leaf	Treatment of piles, menstrual disorder, skin sores	[21]
Acmella oleracea	-	Forest, Meghalaya	Leaf, stem, flower	Treatment of toothache, throat and gum infections, dysentery, rheumatism	[8,9, 25]
Aloe vera	-	Forest, Meghalaya	Stem	Treatment of burn, skin wounds, rashes, insect bites, allergy	[8, 25]
Alstonia scholaris	Thuamriat	Reserve forest, Mizoram	Root, stem	Treatment of malaria, diarrhoea, heart disease, hypertension	[12]
Azadirachta indica	Neem	Wild life sanctuary, Assam	Root, stem, leaf	Treatment of eczema, leprosy, respiratory disorder, infections, ulcer, hypoglycemia	[10]
Centella asiatica	Khliangsyiar, Lbongsyia	Forest, Meghalaya	Leaf, stem, root	Used as a liver tonic, treatment of dysentery, wounds and skin healing in burn areas, high blood pressure	[8,9,25]
Costusspeciosus Sm.	Sumbul	Meghalaya	Rhizome	Treatment of leprosy, tonsillitis, kidney, gall bladder	[19,25]
Curcuma longa	Aieng	National Park, Mizoram	Root, leaf	Treatment of cancer, heart diseases and stomach colic	[12]
Emblica officinalis	Amlokhi	Wild life sanctuary, Assam	Root, stem, leaf	Treatment of ulcer, scabies, dry and wrinkled skin, measles, pediculosis	[10]
Eupatorium odoratum	Tlangsam	Reserve forest, Mizoram	Root, stem	Used as an antiseptic, in removing pinworm from the anus	[12]
Garcinia lancifolia Roxb.	Rupahi-thekera	Assam	Root, leaf, bark	Treatment of dysentery, diarrhoea, fever, stomach problem, jaundice, diabetes, urinary problem	[25]
Houttuynia cordata	JaMyrdoh	Forest, Meghalaya	Root, leaf, stem,	Used in the Treatment of amoebic dysentery, used as an antioxidative, antimutagenic, immunologic and anti-inflammatory agent	[8,9,25]
Litsea cubeba	Sohsyiang	Forest, Meghalaya	Leaf, stem, fruit	Treatment of neuralgic diseases, indigestion, lower back pain	[8,25]
Murraya koenigii	Norosingho	Wild life sanctuary, Assam	Root, stem, leaf	Treatment of dysentery, vomiting, diabetes, wound, microbial infection	[10]
Musa superb Roxb.	Changel	Reserve forest, Mizoram	Flower	Treatment of convulsion, cough, snake bites and bee stings	[12]
Mussaenda roxburghii	Tangmeng	Pasighat, Arunachal Pradesh	Root, stem, leaf	Used as diuretic, anti-pyretic, mushroom poison detoxification	[13]
Potentilla fulgens	Lynniang	Forest, Meghalaya	Root, leaf, stem, flower	Treatment of diabetes, reduces skin inflammation, diarrhoea, used as relief for sore throat	[9,18,25]
Rauwolfia serpentina	Sarpagandha	Wild life sanctuary, Assam	Root, stem, leaf	Treatment of gastrointestinal disorders, diarrhoea, hypertension	[10]
Rubia cordifolia	Sohmisem	Forest, Meghalaya	Leaf, stem	Treatment of lower back pain, headaches, dysentery, cancer, wounds	[8,25]
Terminalia arjuna	Arjun	Wild life sanctuary, Assam	Root, stem, leaf	Used for controlling blood sugar, cardio-tonic, and treatment of cough, diarrhoea, asthma	[10]
Terminalia chebula	Silikha	Wild life sanctuary, Assam	Root, stem, leaf	Treatment of asthma, fever, cough, diarrhea, urinary disease	[10]
Zingiber montanum	Syingblei	Forest, Meghalaya	Leaf, stem, root	Treatment of asthma, rheumatism, joint pain, intestinal disorders	[9,25]

passed from one generation to the other by oral lore as a secret from parent to children[7].

Given this background, this review aims to highlight the diversity, various antimicrobial, antitumor, and antioxidants potential of bacteria associated with plants used as medicine by the ethnic community of NEIHR. It also deals with exploring important endophytes for extraction of the same or related bioactive compound(s) to host plants and various prospects of discovering novel bioactive compounds from a plant endemic to this region.

Diversity and seasonal distribution

NEIHR bacterial endophytes belong to genus *Acinetobacter*, *Bacillus*, *Bulkholderia*, *Leifsonia*, *Microbacterium*, *Microbispora*, *Micrococcus*, *Paenibacillus*, *Pseudomonas*, *Serratia* and *Streptomyces*[8-19]. Among the phylum actinomycetes, majority belong to genus *Streptomyces* followed by *Microbacterium*[10-12,15,17,19,20]. For phylum Firmicutes and Proteobacteria, the majority of them belong to genus *Bacillus, Pseudomonas* and *Serratia*[8,9,13,18,21].

The distribution of endophytic bacteria has been reported mostly in roots followed by stems, leaves and other tissue[10-14]. The population of the endophytic community also differed significantly between the two different sampling seasons, whereby, maximum colonization was observed during summer than in winter[10]. In North East India, the average temperature during summer and winter varies from 18.8°C to 28.5°C and from 11.8°C to 23.2°C, respectively[22]. Barman and Dkhar[19] investigated the influence in the population of endophytic actinobacteria due to seasonal variation in 6 medicinal plants of Meghalaya. Maximum actinobacterial strains were obtained during summer followed by spring, autumn and minimum during winter. Some species were also found to be present solely during the particular season for example; strains *Brevibacterium* sp. and *Saccharopolyspora tripterygii* were isolated from *Solanum khasianum* C.B. Clarke, *Costus speciosus* (J. Koenig) Sm. and *Houttuynia cordata* Thunb during summer but not on other season[19]. Parts of medicinal plants used for isolation of endophytic bacteria are illustrated in Table 1.

Antimicrobial activities

The search for bioactive compounds from bacteria that lives in the tissue of plants has generated a considerable positive impact on human health since they are shown to have inhibitory effect to various pathogens such as *Escherichia coli, Pseudomonas aeruginosa, Salmonella enterica, Streptococcus pyogenes, Staphylococcus aureus*, etc. Various antimicrobial characteristics of the bacterial endophytes of NEIHR are shown in Table 2 and Figure 1.

Antibacterial activities

Nongkhlaw and Joshi[9] studied the antibacterial activity of endophytic bacteria from 10 medicinal plants collected from NEIHR. They observed that the crude metabolites of endophytic isolate *Bacillus subtilis* obtained from *Centella asiatica* inhibit the growth of important human pathogens *S. pyogenes* and *S. aureus*. While the isolate *Serratia marcescens* from the same plant displayed antagonistic activity against *E. coli*. Strains *Bacillus* sp., *Bacillus methylotrophicus*, *Pseudomonas palleroniana* and *Pseudomonas baetica* isolated from *Potentilla fulgens*, *Houttuynia cordata*, *Acmella oleracea*, and *Zingiber montanum* showed antimicrobial activity against *E. coli* and *S. aureus*. Similarly, *Bacillus siamensis* associated with *Litsea cubeba* antagonist the growth of *E. coli* and *S. aureus*.

The crude metabolites extracted using methanol from endophytic *S. marcescens*, *B. subtilis*, *B. methylotrophicus* and *Bacillus* sp. inhibit *S. enterica* ser. *Paratyphi*. The crude metabolites of *S. marcescens* also inhibited *S. pyogenes*. Observation of the activity of the extracts using scanning electron microscopy showed the morphological damages in the cell membrane and cell wall of the test pathogens. The extract of *S. marcescens* causes a detached cell wall and cell burst in *S. pyogenes*. Similarly, cell blisters on the surface, mostly at the polar and septal regions of the *S. enterica* ser. *Paratyphi* cell was observed when the pathogen was treated with the extracts of *S. marcescens*, *B. subtilis* and *methylotrophicus*[18]. *Paenibacillus peoriae* isolated from *Piscidia* spp., an ethnomedicinal plant used by tribal's of Manipur exhibits antibacterial activity against *E. coli*, *B. subtillus*, *S. aureus*, *Pseudomonas fluorescens*, and *Klebsiella pneumonia*[23].

Passari *et al*.[12] studied the antibacterial activity of the endophytic actinobacteria isolated from *Mirabilis jalapa, Alstonia scholaris, Musa superb* Roxb., *C. asiatica, Curcuma longa, Clerodendrum colebrooklanum*, and *Eupatorium odoratum*, 22 strains exhibited antibacterial activity against at least two of the four tested pathogens; *S. aureus*, *P. aeruginosa* and *E. coli*. About two-thirds of the 22 isolates inhibit the growth of all the tested pathogens. All strains demonstrated positive results against *S. aureus* and *E. coli*. *Streptomyces thermocarboxydus* showed activity against *S. aureus* and *E. coli*. *Brevibacterium* sp., which is considered a rare endophytic isolate exhibited antimicrobial activity against *S. aureus* and *P. aeruginosa*.

To study the endophytes possessing antimicrobial potential, Passari *et al.*[17] collected the endemic

Table 2 — Various health beneficial bioactivities of bacterial endophytes of NEIHR

Endophytic isolate	Host plant	Antimicrobial	Tested pathogen	Other bioactivity	Reference
Bacillus sp.	*Houttuynia cordata*	Antibacterial	*Escherichia coli, Staphylococcus aureus,*	Antioxidant	[8-9]
Bacillus siamensis	*Litsea cubeba*	Antifungal	*Emericella nidulans*		[8]
Bacillus subtilis	*Centella asiatica*	Antifungal	*Candida albicans, Emericella nidulans*		[8]
Bacillus subtilis, Serratia marcescens	*Centella asiatica*	Antibacterial	*Escherichia coli, Staphylococcus pyogenes, Staphylococcus aureus*	Antioxidant	[9,18]
Bacillus sp.	*Potentilla fulgens*	Antibacterial	*Escherichia coli, Staphylococcus aureus*		[9]
Pseudomonas palleroniana	*Acmella oleracea*	Antibacterial	*Escherichia coli, Staphylococcus aureus*	Antioxidant	[9]
Streptomyces olivaceus,	*Rhynchotoec-hum ellipticum*	Antibacterial	*Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa*		[17]
Streptomyces sp., *Streptomyces thermocarboxy-dus*	*Rhynchotoec-hum ellipticum*	Antibacterial	*Escherichia coli, Bacillus subtilis*		[17]
Streptomyces sp., *Streptomyces thermocarboxy-dus*	*Rhynchotoec-hum ellipticum*	Antifungal	*Candida albicans*		[17]
Streptomyces olivaceus, Streptomyces thermocarboxy-dus, *Streptomyces* sp.	*Rhynchotoec-hum ellipticum*			Anticancer and antioxidant	[17]
Paenibacilluspeoriae	*Piscidia* spp.	Antibacterial	*Escherichia coli, Bacillus subtillus, Staphylococcus aureus, Pseudomonas fluorescens, Klebsiella pneumonia*		[23]

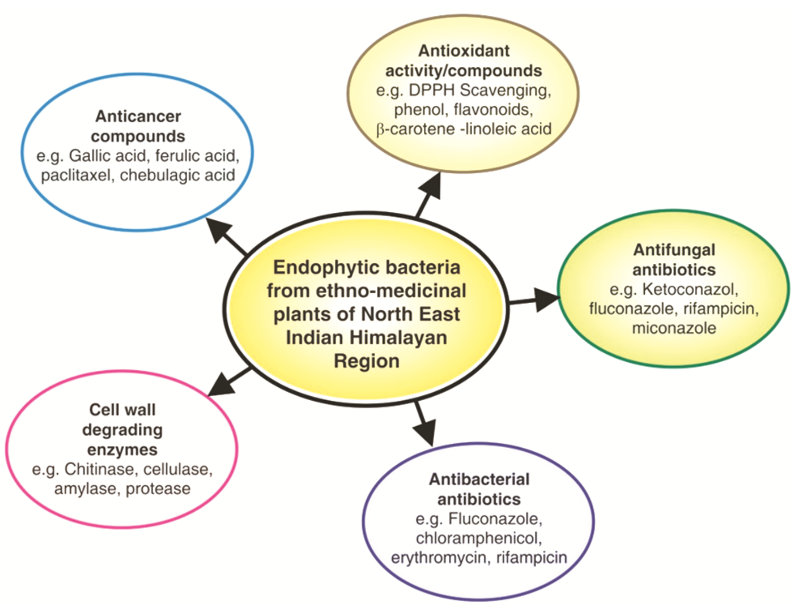

Fig. 1 — Various bioactivities of the endophytic bacteria isolated from NEIHR

medicinal plant *Rhynchotoechum ellipticum* used for the treatment of various types of cancers by ethnic tribes of Mizoram. The authors also studied the production of various important antibiotics by the bioactive strains. All the endophytic bacteria (169) could inhibit *E. coli*. Out of these, 81 isolates showed antibacterial effect to *S. aureus*, *B. subtilis* and *P. aeruginosa*. *Streptomyces olivaceus* displayed maximum antimicrobial potential against *S. aureus* and *P. aeruginosa* whereas; *S. thermocarboxydus*, *Streptomyces* sp. BPSAC101 and *Streptomyces* sp. BPSAC121 showed significant antimicrobial activity against *E. coli* and *B. subtilis*. Majority of the antibacterial activity was shown by *Streptomyces* species. Some of the important antibiotics such as fluconazole, chloramphenicol, erythromycin, ketoconazole, rifampicin, and miconazole were produced by *S. olivaceus* and *Streptomyces* sp.

Gohain *et al.*[10] obtained 76 putative actinomycetes from 6 medicinal plants of Assam to study the diversity and antibacterial activity. *Azadirachta indica, Rauwolfia serpentina* and *Emblica officinalis* were found to be a good habitat for endophytes. The majority of the isolates belong to the genus *Streptomyces* and were found to be present in all the plant species. Of 76 isolates, 21 displayed antimicrobial activity against the tested pathogens. The maximum antibacterial activity against *S. aureus* and *Pseudomonas syringae* was shown by *Microbispora rosea* followed by *Streptomyces antibioticus* against *S. aureus*. Similarly, bacteria isolated from *Garcinia lancifolia* Roxb. of Assam have been reported to inhibit important human pathogens *K. pneumoniae*, *B. subtilis* and *E. coli*[24]

Antifungal activities

Endophytes associated with medicinal plants used by the ethnic community of Meghalaya[25] were isolated to investigate the antimicrobial potential of the bacterial strains. The crude compounds extracted from *B. siamensis* and *B. subtilis* associated with the host plants *Litsea cubeba* and *C. asiatica* respectively, exhibited antagonistic activity against two fungal pathogens *viz*., *Emericella nidulans* and *Candia albicans*[8].

In another study, 22 bacterial isolates associated with *A. cholaris, C. asiatica, C. colebrooklanum, C. longa, E. odoratum, M. jalapa*, and *M. superba* showed an inhibitory effect against *C. albicans*[12]. Bacterial strains *S. thermocarboxydus* and *Streptomyces* sp. BPSAC101 isolated from *R. ellipticum* demonstrated considerable growth inhibition against *C. albicans* by producing antifungal antibiotics ketoconazol, fluconazole, rifampicin, and miconazole[17]. Bacterial isolates isolated from medicinal plants used by the ethnic community of Assam such as *A. indica*, *E. officinalis*, *Garcinia lancifolia* Roxb. *Murraya koenigii*, *R. serpentine*, *Terminalia chebula* and *Terminalia arjuna* are reported to inhibit the growth of *C. albicans*[10,24].

Antioxidant and anticancer activities

Mankind has been exploring ethnomedicinal plants for combating various diseases. Many times, endophytes are assumed to be involved directly or indirectly, in the manufacturing of bioactive compounds by host plants with phytotherapeutic properties. Since endophytes and host plants have a close biological association, they may produce the same or related health beneficial bioactive metabolites as their host plants[26]. For instance, an endophytic fungus *Taxomyces andreanae* can also produce anticancer compound taxol same as their host plant *Taxus brevifolia*[27]. Since endophytes symbiotically live in the tissue of host plants, the bioactive metabolites extracted from them may have very less or not have a negative effect on eukaryotic cells.

Antioxidant activities

There is a vast array of literature reported on antioxidant and antimicrobial potential of the endophytic fungi isolated from ethnomedicinal plants of NEIHR[28-33]. However, there are only a few reports on endophytic bacteria and some of them with antioxidant activities are discussed here. For example, extracts of *S. olivaceus*, *Streptomyces* sp.101, *Streptomyces* sp. 121, and *S. thermocarboxydus* isolated from *R. ellipticum* exhibited DPPH radical scavenging activity[16]. *R. ellipticum* extracts have been reported to exhibit antioxidant, antibacterial and cytotoxic effects[34].

The metabolite extracts isolated from endophytic bacterial strains *Bacillus mycoides*, *Bacillus* sp. *B. subtilis*, *B. methylotrophicus*, *Citrobacter youngae*, *Herminiimonas saxobsidens*, *P. palleroniana, P. baetica*, and *S. marcescens* showed antioxidant properties. The IC_{50} of 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity was in the range of 50 to 20 mg/mL. While the total phenolics and flavonoids produced by these endophytes were in the range of 10.5 to 16.0 and 0.611 to 1.2 mg/g, respectively[9].

The expression of higher antioxidant activity of the plant primed with beneficial endophytic bacteria was demonstrated by Devi *et al*[21]. The authors injected the non-pathogenic strain *P. aeruginosa* having plant growth promoting (PGP) traits into the host plant *Achyranthes aspera* L. and studied the antioxidant activity and compared it with the untreated plant. Bioinoculant-treated plants reveal higher DPPH radical scavenging activity with IC_{50} value of 6.41 mg/mL, while the control plant showed 8.11 mg/mL. Similarly, higher β-Carotene-linoleic acid content was found in plants inoculated with the endophytic strain *P. aeruginosa*. Bioinoculant-treated plant leaf extract also showed higher reducing power than that of the control plant. The values ranged from 0.452 to 1.122% in the inoculated plant but in the control plant, the values were found in the range from 0.342 to 0.951%.

Anticancer activities

NEIHR is becoming the cancer hub of the country. The most common cancer in the region is the esophagus, stomach, lung, and breast caused by the consumption of tobacco, smoked meat and fermented vegetables[35,36]. The leaf decoction of *R. ellipticum* is consumed orally for treating various types of cancers by ethnic tribes of Mizoram. Passari *et al*.[17] studied the anticancer and antioxidant compounds present in the extract of bioactive isolates showing good antimicrobial activities. An anticancer compound, Gallic acid (3,4,5-trihydroxybenzoic acid) was detected in 4 bioactive strains *S. olivaceus*, *S. thermocarboxydus*, *Streptomyces* sp. BPSAC101, and *Streptomyces* sp. BPSAC121. Gallic acid is a phenolic compound that can induce cell apoptosisin several types of cancer cells such as lung and prostrate[37,38]. Another antitumor compound phenolic ferulic acid was quantified in *Streptomyces* sp. BPSAC 121. The compound has been reported to possess antitumor activity by promoting apoptosis, inducing cell arrest and autophagy of breast, liver, cervical, and colon cancer cells[39,40]. Additionally, paclitaxel an anticancer compound used was extracted from *S. olivaceus* (23.4 µg/g), *Streptomyces* sp. BPSAC101 (18.2 µg/g) and *Streptomyces* sp. BPSAC121 (10.2 µg/g). Paclitaxel inhibits the growth of cancer cells by polymerization of microtubules thereby blocking the progression of mitosis. It also induces cytotoxicity to cancer cells in a time and concentration-dependent manner[41,42]. Due to its ability to arrest cell cycle, it can act synergistically when combined with radiation[43]. The supernatants of *S. olivaceus* and *Streptomyces* sp. BPSAC121 was detected for the presence of anticancer compound, chebulagic acid (CA). CA has been reported to show broad-spectrum anticancer effects on colon cell lines, inhibit cell growth, and induce apoptosis in retinoblastoma cells[44].

Biosynthetic gene clusters (BGCs)

Biosynthetic gene clusters comprise two or more genes clustered in a group that collectively encode a biosynthetic pathway for the production of a secondary metabolite. The major structural classes of BGCs are non-ribosomal peptide synthetases (NRPS), polyketide synthases (PKS), terpenes, and bacteriocins. Among these NRPS and PKS are the most targeted gene clusters[45]. Some of the endophytes isolated from NEIHR were studied for the presence of NRPS and PKS gene clusters. For instance**,** Passari *et al*.[12] have reported biosynthetic gene clusters PKSI (Polyketide synthase Type I) and NRPS (Nonribosomal Peptide Synthetase) in 23 endophytic isolates of which, 10 isolates displayed PKS type I while 13 isolates displayed NRPS gene cluster. The majority of the endophytic strains that displayed the presence of antibiotic synthetic genes belong to the genus *Streptomyces*. Further Passari *et al*.[17] have investigated 81 bioactive endophytes isolated from a medicinal plant *R. ellipticum*. Of these strains, PKSI was found in 25 strains, PKSII in 41 strains, and NRPS in 32 strains. Similarly, Gohain *et al*.[10] demonstrated the presence of PKSII in 18 endophytic strains and PKSI in 3 strains. Genus *Streptomyces* was found to be the most prominent bioactive strain inhibiting against most of the pathogens and also displayed the highest biosynthetic gene cluster.

Unexplored medicinal plants of NEIHR

Since there is a high chance of discovering the same and or novel bioactive metabolite present in plants from the associated endophytes, it is noteworthy to highlight some of the medicinal plants used by the ethnic community for treating the common diseases of the region. This will help in the selection of the plants for isolation, study on the mitigation of the disease and identification of endophytes having health-beneficial activities. As endophytes are closely associated with the host plants, there is great potential to discover bioactive compounds that may be less toxic to eukaryotic cells due to their close association with plants. Endophytes may also produce the same health-beneficial compounds as the host plant due to gene transfer between the host and bacteria[27].

Cancer, malaria and tuberculosis are the three most prevalent diseases in NEIHR[46,47] and many plants in this region have been documented for combating such diseases. Medicinal plants *viz*., *A. aspera, Adhatoda vasica, Ageratum conyzoides, Clerodendrum infortunatum, Croton tiglium, C. longa, Leonurus japonicas, Mikania micrantha, Panax ginseng, Paris polyphylla, Phyllanthus emblica, P. fulgens, R. ellipticum* and *Vitex trifolia* used by ethnic people of NEIHR for treating cancer have been documented to demonstrate cytotoxic/anti-tumor activity against human cancer cell lines *in vitro* and *in vivo* conditions[48-61]. Ginsenosides, anti-cancer compounds present in *P. ginseng* induce apoptosis and inhibit the proliferation of tumor cells. It also inhibits the invasion of tumor cells to different tissue and the development of metastasis[62]. Yan *et al*.[63] investigated the endophytic bacteria associated with *P. ginseng* plant and found that *Agrobacterium* sp. could produce various ginsenoside compounds in high quantities. Endophytic bacteria isolated from the same plant have also been reported to enhance the accumulation of ginsenoside in ginseng plant[64]. From the above scientific research findings, further exploration needs to be done to discover important anti-cancer compounds for application in pharmaceutical industries from bioactive endophytes that can produce the same or related anti-cancer compounds as host plants.

Endophytic *Streptomyces* sp. obtains from *Shorea ovalis* tree used by the native of Malaysia for treating malaria showed the ability to inhibit the growth of *Plasmodium berghei*. Treatment of the crude metabolites protects the disease development in mice infected with the parasites[65]. Similarly, bioactive compounds; cyclohexane, butyl propyl ester and 2,3-hepanedione produced by endophyte *Streptomyces* sp. demonstrate growth inhibition against *P. berghei* larva[66]. The anti-plasmodium activity of the common medicinal plants used by the ethnic people of Northeast, has been reported in the literature[67-73]. However, no systemic scientific study has been done on the mitigation of malarial disease by ethnomedicinal plants of NEIHR. Systematic study of the antimalarial activity of these medicinal plants and also a further investigation on the endophytes colonising in their inner tissue for a similar activity to fully realised the therapeutic potential of the plants used by the ethnic community of the region.

The commonly used medicinal plants for treating tuberculosis by ethnic communities of NEIHR such as *A. vasica, C. asiatica, Cinnamomum zeylanicum, Nasturtium officinale, P. ginseng,* and *V. trifolia* have been reported to exhibit anti-tuberculosis activity[74-79]. Growth inhibition of *Mycobacterium tuberculosis* strains by fungi isolated from *C. asiatica, C. zeylanicum* have also been reported[30,80]. However, there are limited reports on antimycobacterial activity of bacteria associated with such medicinal plants. Further investigation for antimycobacterial activities of such plants documented for treating tuberculosis by the people of NEIHR and the endophytes need to be done, since, scientific evidence for mitigation of the disease has not been reported.

Future perspectives and Conclusions

Some of the important ethnomedicinal plants have been included in the well-documented medicines based on the scientific shreds of evidence of medicinal properties[81]. However, many of the folk medicinal plants remain endemic to a certain part of the region and further exploration and/ scientific research is needed to extract and identify the bioactive compound for pharmacological application. Hence, to mitigate the emergence of drug-resistant pathogens to conventional antibiotics with less adverse effects, there is a need to explore for unusual bacteria having a new and novel mechanism of action in containing the diseases. The need of the hour is to explore the bacteria that live in the tissue of plants growing in under and or unexplored ecosystems, peculiar endemic regions, extreme ecosystems[82,83]. There is a possibility of isolating billions of bacteria since about 30,000 different plant species have been discovered and each plant (in billions) is expected to be associated with one or more beneficial bacteria[84]. Interestingly, only 1 to 2% of the plant species have been studied for association with endophytes[83].

Since NEIHR is endowed with diverse ecosystems there is a need to further explore health beneficial endophytic bacteria from unexplored or underexplored sources endemic to NEIHR for extracting a new bioactive compound from the novel bacteria that can find application in pharmaceutical and other important industries.

For large scale extraction of bioactive metabolites from plants, large quantities are required and continuous production is not possible as plants are slow-grower and are found only in a particular region. To supply human needs, plant tissue culture may offer a solution however; the techniques may not be feasible due to high cost[85]. Since endophytes and host plants have a close biological association, they may produce the same or related health beneficial bioactive metabolites as their host plants. Extraction of compounds using endophytic bacteria for large-scale production will be comparatively easier, cost-effective and can be done in a short period which will also save the endemic medicinal plants from overexploitation.

As indicated earlier, there are vast arrays of research literature reports on the antimicrobial, cytotoxicity and antioxidant activities of fungi isolated from medicinal plants of NEIHR. However, reports on the same from endophytic bacteria are scanty. Researchers need to study the bioactivity of the endophytic bacteria isolated from ethnomedicinal plants used by the ethnic healers to prove the health claim of treating various diseases especially tuberculosis, and cancer which are common in India, particularly in NEIHR. They also need to search for bioactive compounds that can mitigate mosquito-borne diseases such as Japanese encephalitis, malaria and dengue which are common in the region[86]. Researchers must take urgent initiatives to extract, identify and understand the underlying molecular mechanisms of action of the compound that facilitated the mitigation of the disease to control the rise in multi-drug resistant pathogens. The therapeutic potential of endophytes has not been fully realized by the pharmaceutical industry. Hence, the preliminary works which have been successfully carried out *in-vitro* need to be carried forward for their *in-vivo* appraisal including a clinical trial. Endophytic bacteria hold a good promise for the discovery of novel bioactive compounds of pharmaceutical importance which in turn will ensure healthy living.

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Conflict of Interest

The authors declare no known conflict of interests.

Authors' Contributions

KT perceived and wrote the original manuscript. PK, AKD, HNS, CR, TSS, PL and TL assisted in the literature survey and construction of tables and figures. SKS, MAA and SD assisted in manuscript editing. SSR assist, delivered critical feedback and approved the final manuscript.

References

1 Myers N, Mittermeier R A, Mittermeier C G, da Fonseca G A B & Kent J, Biodiversity hotspots for conservation priorities, *Nature*, 403 (2000) 853-858.

2 Kalita N, Resolving ethnic conflict in Northeast India, *Proc Indian Hist Congr*, 72 (2011) 1354-1367.

3 Stan D, Enciu A-M, Mateescu A l, Ion A C, Brezeanu A C, *et al*., Natural compounds with antimicrobial and antiviral effect and nanocrriers used for their transportation, *Front Pharmacol*, 12 (2021) 723233.

4 Demain A L & Sanchez S, Microbial drug discovery: 80 Years of progress, *J Antibiot*, 62 (2009) 5-16.

5 Liu X, Ashforth E, Ren B, Song F, Dai H, *et al*., Bioprospecting microbial natural product libraries from the marine environment for drug discovery, *J Antibiot*, 63 (8) (2010) 415-422.

6 Milshteyn A, Schneider J S & Brady S F, Mining the metabiome: identifying novel natural products from microbial communities, *Chem Biol*, 21 (9) (2014) 1211-1223.

7 Köberl M, Schmidt R, Ramadan E M, Bauer R & Berg G, The microbiome of medicinal plants : diversity and importance for plant growth, quality and health, *Front Microbiol*, 4 (2013) 400.

8 Nongkhlaw F M W & Joshi S R, Epiphytic and endophytic bacteria that promote growth of ethnomedicinal plants in the subtropical forests of Meghalaya, India, *Rev Biol Trop*, 62 (4) (2014) 1295.

9 Nongkhlaw F M W & Joshi S R, Investigation on the bioactivity of culturable endophytic and epiphytic bacteria associated with ethnomedicinal plants, *J Infect Dev Ctries*, 9 (9) (2015) 954-961.

10 Gohain A, Gogoi A, Debnath R, Yadav A, Singh B P, *et al*., Antimicrobial biosynthetic potential and genetic diversity of endophytic actinomycetes associated with medicinal plants, *FEMS Microbiol Lett*, 362 (19) (2015) 1-10.

11 Passari A K, Mishra V K, Gupta V K, Yadav M K, Saikia R, *et al*., *In vitro* and *in vivo* plant growth promoting activities and DNA fingerprinting of antagonistic endophytic actinomycetes associates with medicinal plants, *PLoS One*, 10 (9) (2015) 1-18.

12 Passari A K, Mishra V K, Saikia R, Gupta V K & Singh B P, Isolation, abundance and phylogenetic affiliation of endophytic actinomycetes associated with medicinal plants and screening for their *in vitro* antimicrobial biosynthetic potential, *Front Microbiol*, 6 (2015) 273.

13 Pandey P K, Samanta R & Yadav R N S, Plant beneficial endophytic bacteria from the ethnomedicinal *Mussaenda roxburghii* (Akshap) of Eastern Himalayan province, India, *Adv Biol*, 2015 (2015) 1-8.

14 Devi K A, Pandey P & Sharma G D, Plant growth-promoting endophyte *Serratia marcescens* al2-16 enhances the growth of *Achyranthes aspera* l., a medicinal plant, *HAYATI J Biosci*, 23 (2016) 173-180.

15 Passari A K, Mishra V K, Gupta V K, Saikia R & Singh B P, Distribution and identification of endophytic *Streptomyce*s species from *Schima wallichii* as potential biocontrol agents against fungal plant pathogens, *Polish J Microbiol*, 65 (3) (2016) 319-329.

16 Passari A K, Mishra V K, Leo V V, Gupta V K & Singh B P, Phytohormone production endowed with antagonistic potential and plant growth promoting abilities of culturable endophytic bacteria isolated from *Clerodendrum colebrookianum* Walp, *Microbiol Res*, 193 (2016) 57-73.
17 Passari A K, Mishra V K, Singh G, Singh P, Kumar B, *et al*., Insights into the functionality of endophytic actinobacteria with a focus on their biosynthetic potential and secondary metabolites production, *Sci Rep*, 7 (2017) 11809.
18 Nongkhlaw F M W & Joshi S R, Microscopic study on colonization and antimicrobial property of endophytic bacteria associated with ethnomedicinal plants of Meghalaya, *J Microsc Ultrastruct*, 5 (2017) 132-139.
19 Barman D & Dkhar M S, Seasonal variation influence endophytic actinobacterial communities of medicinal plants from tropical deciduous forest of Meghalaya and characterization of their plant growth-promoting potentials, *Curr Microbiol*, 77 (2020) 1689-1698.
20 Momin M D & Tripathi S K, Studies of endophytic actinomycetes associated with medicinal plants of Mizoram, Northeast, India, *Int J Curr Microbiol Appl Sci*, 7 (12) (2018) 1398-1407.
21 Devi K A, Pandey G, Rawat A K S, Sharma G D & Pandey P, The endophytic symbiont-*Pseudomonas aeruginosa* stimulates the antioxidant activity and growth of *Achyranthes aspera* L, *Front Microbiol*, 8 (2017) 1897.
22 Chakraborty D, Saha S, Singh R K, Sethy B K, Kumar A, *et al.*, Trend analysis and change point detection of mean air temperature: A spatio-temporal perspective of North-Eastern India, *Environ Process*, 4 (2017) 937-957.
23 Ngashangva N, Devi I S & Kalita M C, Screening of endophytes from traditionally used medicinal plants of Manipur for their antimicrobial activity an impact towards future drug discovery, *Int J Sci Res Biol Sci*, 6 (5) (2019) 39-47.
24 Doley P & Jha D K, Antimicrobial activity of bacterial endophytes from medicinal endemic plant *Garcinia lancifolia* Roxb, *Ann Plant Sci*, 4.12 (2015) 1243-1247.
25 Hynniewta S R & Kumar Y, Herbal remedies among the Khasi traditional healers and village folks, *Indian J Tradit Know*, 7 (4) (2008) 581-586.
26 Golinska P, Wypij M, Agarkar G, Rathod D, Dahm H *et al*., Endophytic actinobacteria of medicinal plants: diversity and bioactivity, *Antonie Van Leeuwenhoek*, 108 (2) (2015) 267-289.
27 Stierle A, Strobel G & Stierle D, Taxol and taxane production by taxomyces andreanae, an endophytic fungus of Pacific Yew, *Science*, 260 (5105) (1993) 214-216.
28 Gogoi D K, Deka Boruah H P, Saikia R & Bora T C, Optimization of process parameters for improved production of bioactive metabolite by a novel endophytic fungus *Fusarium* sp. DF2 isolated from *Taxus wallichiana* of North East India, *World J Microbiol Biotechnol*, 24 (2008) 79-87.
29 Bhagobaty R K & Joshi S R, Antimicrobial and antioxidant activity of endophytic fungi isolated from ethnomedicinal plants of the “Sacred forests” of Meghalaya, India, *Mikol Lek*, 19 (1) (2012) 5-11.
30 Nath A, Pathak J & Joshi S R, Diversity and biological activities of endophytic fungi of *Emblica officinalis*, an ethnomedicinal plant of India, *Mycobiology*, 40 (1) (2012) 8-13.
31 Nongalleima K, Dey A, Deb L, Singh C B, Thongam B, *et al*., Endophytic fungus isolated from *Zingiber zerumbet* (L.) Sm. inhibits free radicals and cyclooxygenase activity, *Int J Pharm Tech Res*, 5 (2) (2013) 301-307.
32 Devi N N& Singh M S, Bioactivity of endophytic fungus *Colletotrichum gloeosporioides* isolated from *Phlogacanthus thyrsiflorus* Nees, *Int Res J Biol Sci*, 3 (2014) 97-99.
33 Deka D & Jha D K, Antimicrobial activity of endophytic fungi from leaves and barks of *Litseacubeba* Pers., a traditionally important medicinal plant of North East India, *Jordan J Biol Sci*, 11 (1) (2018) 73-79.
34 Chaudhuri K, Hasan S K N, Barai A C & Das S, Nutraceutical evaluation of *Rhynchotechum ellipticum*, a potent wild edible plant consumed by the tribal of North-Eastern region in India and green synthesis of gold nanoparticles using its leaf extract, *J Pharmacogn Phytochem*, 7 (3) (2018) 1434-1442.
35 Sharma J D, Kalit M, Nirmolia T, Saikia S P, Sharma A, *et al*., Cancer: Scenario and relationship of different geographical areas of the globe with special reference to North East-India, *Asian Pacific J Cancer Prev*, 15 (8) (2014) 3721-3729.
36 Shanker N, Mathur P, Das P, Sathishkumar K, Shalini A J M, *et al*., Cancer scenario in North-East India and need for an appropriate research agenda, *Indian J Med Res*, 154 (2021) 27-35.
37 Ohno Y, Fukuda K, Takemura G, Miki T, Motohiro W, *et al*., Induction of apoptosis by gallic acid in lung cancer cells, *Anticancer Drugs*, 10 (1999) 845-852.
38 Chen H M, Wu Y C, Chia Y C, Chang F R, Hsu H K, *et al*., Gallic acid, a major component of *Toona sinensis* leaf extracts, contains a ROS-mediated anti-cancer activity in human prostate cancer cells, *Cancer Lett*, 286 (2) (2009) 161-171.
39 Eroğlu C, Seçme M, Bağcı G & Dodurga Y, Assessment of the anticancer mechanism of ferulic acid via cell cycle and apoptotic pathways in human prostate cancer cell lines, *Tumour Biol J Int Soc Oncodevelop Biol Med*, 36 (12) (2015) 9437-9446.
40 Panwar R, Sharma A K, Kaloti M, Dutt D & Pruthi V, Characterization and anticancer potential of ferulic acid-loaded chitosan nanoparticles against ME-180 human cervical cancer cell lines, *Appl Nanosci*, 6 (2016) 803-813.
41 Horwitz S B, Lothstein L, Manfredi J J, Mellado W, Parness J, *et al*., Taxol: mechanisms of action and resistance, *Ann N Y Acad Sci*, 466 (1986) 733-744.
42 Tishler R B, Schiff P B, Geard C R & Hall E J, Taxol: A novel radiation sensitizer, *Int J Radiat Oncol*, 22 (1992) 613-617.
43 Weaver B A, How Taxol/paclitaxel kills cancer cells, *Mol Biol Cell*, 25 (2014) 2677-2681.
44 Kumar N, Gangappa D, Gupta G & Karnati R, Chebulagic acid from *Terminaliachebula* causes G1 arrest, inhibits NFκB and induces apoptosis in retinoblastoma cells, *BMC Complement Altern Med*, 14 (2014) 319.
45 Chen R, Wong H L, Kindler G S, MacLeod F I, Benaud N *et al*. Discovery of an Abundance of Biosynthetic Gene Clusters in Shark Bay Microbial Mats. *Front Microbiol*, 11 (2020) 1950.
46 Sharma V P, Dev V & Phookan S, Neglected *Plasmodium vivax* malaria in northeastern States of India, *Indian J Med Res*, 141 (5) (2015) 546-555.

47 Kayina T K P, Tarao M S & Nula P, Tuberculosis in North-East India : patient profile and treatment outcome of patient attending RNTCP, *Int J Community Med Public Heal*, 6 (7) (2019) 2856-2860.

48 Yan L L, Zhang Y J, Gao W Y, Man S L & Wang, *In vitro* and *in vivo* anticancer activity of steroid saponins of *Paris polyphylla* var. Yunnanensis, *Exp Oncol*, 31 (1) (2009) 27-32.

49 Subbarayan P R, Sarkar M, Impellizzeri S, Raymo F, Lokeshwar B L, *et al*., Anti-proliferative and anti-cancer properties of *Achyranthes aspera*: specific inhibitory activity against pancreatic cancer cells, *J Ethnopharmacol*, 131 (1) (2010) 78-82.

50 El-Sayed M M, El-Hashash M M, Mohamed M A & Korany T M, Cytotoxic activity of *Vitex trifolia* purpurea extracts, *J Egypt Soc Parasitol*, 41 (2) (2011) 409-416.

51 Shahid-Ud-Duala A F M, Siddiqui R, Alam M M & Hossain M A, Studies on the antimicrobial and brine shrimp toxicity of the leaves extract of *Ageratum conyzoides*, *Bangladesh J Microbiol*, 29 (2) (2012) 98-103.

52 Mahata S, Pandey A & Shukla S, Anticancer activity of *Phyllanthus emblica* Linn. (Indian gooseberry): inhibition of transcription factor AP-1 and HPV gene expression in cervical cancer cells, *Nutr Cancer*, 65 (S1) (2013) 88-97.

53 Zhang X L, Wang L, Li F, Yu K & Wang M-K, Cytotoxic phorbol esters of *Croton tiglium*, *J Nat Prod*, 76 (2013) 858-864.

54 Dou X, Zhang Y, Sun N, Wu Y & Li L, The anti-tumor activity of *Mikania micrantha* aqueous extract *in vitro* and *in vivo*, *Cytotechnology*, 66 (2014) 107-117.

55 Duraipandiyan V, Al-Dhabi N A, Balachandran C, Ignacimuthu S, Sankar C, *et al*., Antimicrobial, antioxidant, and cytotoxic properties of vasicine acetate synthesized from vasicine isolated from *Adhatoda vasica* L, *Biomed Res Int*, 2015 (2015) 727304.

56 Haris M I R, Mahmood R, Rahman H & Rahman N, *In vitro* cytotoxic activity of *Clerodendrum infortunatum* L. against T47D, PC-3, A549 and HCT-116 human cancer cell lines and its phytochemical screening, *Int J Pharm Pharm*, 8 (1) (2016) 439-444.

57 Nagahama K, Utsumi T, Kumano T, Maekawa S, Oyama N, *et al*., Discovery of a new function of curcumin which enhances its anticancer therapeutic potency, *Sci Rep*, 6 (2016) 30962.

58 Filipiak-Szok A, Kurzawa M, Szłyk E, Twaruzek M, Blajet-Kosicha A, *et al*., Determination of mycotoxins, alkaloids, phytochemicals, antioxidants and cytotoxicity in *Asiatic ginseng* (Ashwagandha, Dong quai, Panax ginseng), *Chemzvesti*, 71 (2017) 1073-1082.

59 Faysal M, Azad A K, Islam F, Rahman MM, Hossain MS, *et al*., Phytochemical investigation, cytotoxic and thrombolytic activity of acetone extracts of *Rhynchotechum ellipticum* (Gesneriaceae), *Pharmacol online*, 2 (2019) 190-198

60 Ganguly B, Chaudhary A, Dakhar H, Singh I P & Chatterjee A, Methanolic extract of *Potentilla fulgens* root and its ethyl-acetate fraction delays the process of carcinogenesis in mice, *Sci Rep*, 9 (2019) 16985.

61 Jiang M, Hu Y, Jiao L, Dong P, Yin S, *et al*., A new labdane-type diterpenoid from *Leonurus japonicus*, *J Asian Nat Prod Res*, 21 (7) (2019) 627-632.

62 Nag S A, Qin J-J, Wang W, Wang M-H, Wang H, *et al*., Ginsenosides as anticancer agents: *in vitro* and *in vivo* activities, structure-activity relationships, and molecular mechanisms of action, *Front Pharmacol*, 3 (2012) 25.

63 Yan H, Jin H, Fu Y, Yin Z & Yin C, Production of rare ginsenosides rg3 and rh2 by endophytic bacteria from *Panax ginseng*, *J Agric Food Chem*, 67 (31) (2019) 8493-8499.

64 Song X, Wu H, Yin Z, Lian M & Yin C, Endophytic bacteria isolated from *Panax ginseng* improves ginsenoside accumulation in adventitious ginseng root culture, *Molecules*, 22 (6) (2017) 837.

65 Baba M S, Zin N M, Hassan Z A A, Latip J, Pethick F, *et al*., *In vivo* antimalarial activity of the endophytic actinobacteria, *Streptomyces* SUK 10, *J Microbiol*, 53 (12) (2015) 847-855.

66 Zin N M, Remali J, Nasrom M N, Ishak S A, Baba M S, *et al*., Bioactive compounds fractionated from endophyte *Streptomyces* SUK 08 with promising ex-vivo antimalarial activity, *Asian Pac J Trop Biomed*, 7 (12) (2017) 1062-1066.

67 Gandhi M & Vinayak V K, Preliminary evaluation of extracts of *Alstoniascholaris* bark for in vivo antimalarial activity in mice, *J Ethnopharmacol*, 29 (1990) 51-57.

68 Sharma S K, Satyanarayana S, Yadav R N & Dutta L P, Screening of *Coptisteeta* Wall. for antimalarial effect: a preliminary report, *Indian J Malariol*, 30 (3) (1993) 179-181.

69 Bhat G P & Surolia N, *In vitro* antimalarial activity of extracts of three plants used in the traditional medicine of India, *Am J Trop Med Hyg*, 65 (4) (2001) 304-308.

70 Bamunuarachchi G S, Ratnasooriya W D, Premakumara S & Udagama PV, Antimalarial properties of *Artemisia vulgaris* L. ethanolic leaf extract in a *Plasmodium berghei* murine malaria model, *J Vector Borne Dis*, 50 (2013) 278-284

71 Inbaneson S J, Sundaram R & Suganthi P, *In vitro* antiplasmodial effect of ethanolic extracts of traditional medicinal plant *Ocimum* species against *Plasmodium falciparum*, *Asian Pac J Trop Med*, 5 (2012) 103-106.

72 Widyawaruyanti A, Asrory M, Ekasari W, Setiawan D, Radjaram A, *et al*., *In vivo* antimalarial activity of *Andrographis paniculata* tablets, *Procedia Chem*, 13 (2014) 101-104.

73 Swain S S, Sahu M C & Padhy R N, In silico attempt for adduct agent(s) against malaria: Combination of chloroquine with alkaloids of *Adhatoda vasica*, *Comput Methods Programs Biomed*, 122 (1) (2015) 16-25.

74 Suresh M, Rath P K, Panneerselvam A, Dhanasekaran D & Thajuddin N, Anti-mycobacterial effect of leaf extract of *Centella asiatica* (Mackinlayaceae), *Res J Pharm Technol*, 3 (3) (2010) 872-876.

75 Gupta R, Thakur B, Singh P, Singh H B, Sharma V D, *et al*., Anti-tuberculosis activity of selected medicinal plants against multi-drug resistant *Mycobacterium tuberculosis* isolates, *Indian J Med Res*, 131 (2010) 809-813.

76 Tiwari N, Thakur J, Saikia D & Gupta M M, Antitubercular diterpenoids from *Vitex trifolia*, *Phytomedicine*, 20 (2013) 605-610.

77 Quezada-Lázaro R, Fernández-Zuñiga E A, García A, Garza-González E, Alvarez L, *et al*., Antimycobacterial compounds from *Nasturtium officinale*, *Afr J Tradit Complement Altern Med*, 13 (2) (2016) 31-34.

78 Irianti T, Pratiwi S U T, Kuswandi, Tresnaasih N, Cahya D, *et al*., Anti-tuberculosis activity of extract ethyl

acetate kenikir leaves (*Cosmos caudatus* H.B.K) and sendok leaves (*Plantago major* L.) by *in vitro* test, *Trad Med J*, 23 (2018) 1-8.

79 Mota A P P, Campelo T A, & Frota C C, Evaluation of the antimicrobial activity of *Cinnamomum zeylanicum* essential oil and trans-cinnamaldehyde against resistant *Mycobacterium tuberculosis*, *Biosci J*, 35 (1) (2019) 296-306.

80 Cheng M-J, Wu M-D, Yanai H, Su Y-S, Chen I-S, *et al*., Secondary metabolites from the endophytic fungus *Biscogniauxia formosana* and their antimycobacterial activity, *Phytochem Lett*, 5 (2012) 467-472.

81 Dutta B & Dutta P, Potential of ethnobotanical studies in North East India: An overview, *Indian J Tradit Know*, 4 (1) (2005) 7-14.

82 Strobel G & Daisy B, Bioprospecting for microbial endophytes and their natural products, *Microbiol Mol Biol Rev*, 67 (4) (2003) 491-502.

83 Strobel G, The emergence of endophytic microbes and their biological promise, *J Fungi* (*Basel*), 4 (2) (2018) 57.

84 Strobel G, Daisy B, Castillo U & Harper J, Natural products from endophytic microorganisms, *J Nat Prod*, 67 (2) (2004) 257-268.

85 Castillo U F, Strobel G A, Mullenberg K, Condron M M, Teplow D B, *et al*., Munumbicins E-4 and E-5: Novel broad-spectrum antibiotics from *Streptomyces* NRRL 3052, *FEMS Microbiol Lett*, 255 (2006) 296-300.

86 Dev V, Sharma V & Barman K, Mosquito-borne diseases in Assam, north-east India: current status and key challenges, *WHO South-East Asia J Public Heal*, 4 (1) (2015) 20.