A Review on Medicinal Plants Having Anticancer Properties of Northeast India and Associated Endophytic Microbes and their Future in Medicinal Science

Sanjib Kalita¹, Anindita Sarma¹, Ankur Hazarika²*, Satarupa Hazarika³, Saranga Pani Saikia⁴ and Dibyajyoti Kalita⁴

¹Department of Botany, Gauhati University, Guwahati - 781 014, Assam, India.
²Department of Zoology, Gauhati University, Guwahati - 781 014, Assam, India.
³Handique Girls’ College, Guwahati - 781 001, Assam, India.
⁴Department of Zoology, Assam Don Bosco University, Sonapur - 782 402, Assam, India.

Abstract

Human beings are affected by different diseases and suffer to different extents. Cancer is one of the major human disease and millions of people suffered from cancer and end their lives every year. Peoples are dependent on herbal medicines since prehistoric time especially from developing countries. It is very common to have different side effects of modern synthetic medicines; hence now-a-days importance of herbal medicines due to no or least side effects increases all parts of the world. But the major problems of using herbal medicines are that plants can produce very limited amount of medicinally important bioactive metabolites and they have very long growth periods. Therefore endophytes are the excellent alternative of plant derived metabolites. Endophytic microbes can synthesize exactly same type of metabolites as the plant produces. North East India is a treasure of plant resources; various types of medicinal plants are present in this region. Different types of indigenous tribes are inhabited in this region who used different plants in traditional system for treating various disease. But with increasing demand it is sometimes not sufficient to manage the demand of medicines, therefore for massive production endophytic study is crucial. In spite of having huge plant resources very limited endophytic studies are observed in this region. In this review, we studied different plants with their endophytes of NE India showing anticancer properties.

Keywords: Medicinal Plants, Anticancer Agent, Secondary Metabolites, Endophytes

*Correspondence: ankurhazarika910@gmail.com
INTRODUCTION

Cancer is one of the major challenges and is one of the leading causes of death globally. According to the International Agency for Research on Cancer, the incidence of mortality and prevalence of major forms of cancer in 184 countries across the globe revealed that there were 8.2 million people lost their lives and 14.1 million new cancer cases across the world annually, and it was estimated that there will be 26 million people newly get infected and 17 million people will die due to cancer per year by 2030.1 Again according to Cancer Research UK 9.6 million people ended up their lives out of 17 million people suffered from cancer in 2018 and they expected that by 2040 about 27.5 million new cancer patients in each year if this increasing trend will continue.2 In cancer the control of growth is lost in one or more cells which lead to either solid mass of cells called tumour or to a liquid cancer like blood or bone marrow related cancers.3 Cancer is not a single disease, it is a group of disease all showing unregulated cell growth and originated due to abnormal functions of genes. Cancer cells can invade nearby tissues or it can spread via lymphatic system or blood to distant part of the body.4,5 A typical cancer cell has the ability to invasion and angiogenesis and they overcome apoptosis.6 In the process of transformation of normal cell to malignant cell sequence of events takes place which results accumulation of genetic instabilities in a cell. Genetic instability leads to mutations, if these mutations take place in oncogenes, tumour suppressor genes, DNA repair genes, apoptotic genes lead to development of cancer.5 Surgery, chemotherapy and radiotherapy are the three main treatment strategy involved in cancer treatment.7 Chemotherapy is the most effective method of cancer treatment, it uses low molecular weight drugs to selectively destroy or reduce their proliferation rate of tumour cells. There are some disadvantages of chemotherapy are also commonly observed, bone marrow suppression, gastrointestinal tract lesions, nausea, hair loss and clinical resistance are some side effects of chemotherapy due to the toxicity to both tumour cells as well as healthy cells of the cytotoxic agents used in chemotherapy.8,9 For reducing these side effects different plants and plant products are alternative ways for cancer treatment. Plants are very rich source of various secondary metabolites, which shows different medicinal properties. It has been reported potential anticancer/antitumor properties in various plant extracts, therefore these plant species can be used as safe and effective drugs for treating cancer.9,10

North-East India is one of the biodiversity hotspots which is located between 22–30°N latitude and 89–97°E longitude. This region is very rich in plant resources due to diversified topography and climatic conditions. High rainfall, moderate temperature and high humidity and marshes are characteristics in this region, which favors diversified species and wide range of vegetation from tropical to alpine forests.11 North-East India is topographically mostly hilly and is occupied by different tribes. These ethnic tribal communities mainly depend on herbal medicines for their healthcare needs as they have no adequate knowledge on modern medicines.12,13 The most challenging part of adapting herbal medicine is that in most cases plant can produce these medicinally important bioactive secondary metabolites in very low amount, long growth periods of plants and difficulty in separating the required compound from other compounds.14 Therefore, with the increasing demand to provide required amount of compounds exploitation of natural resources frequently happen. Therefore, for balancing both aspects i.e., production of sufficient amount of pharmacologically active compounds as well as conservation of natural resources without exploitation, scientist thought alternative ways, they exploit the ability of endophytic microbes to synthesize various bioactive secondary metabolites which shows exactly similar properties with the plant derived bioactive compounds.15 Endophytes are quite common in vascular plants, and are present almost every vascular plant of this planet.16 In 1866 De Barry for the first time coined the term endophytes.17 It has great importance to study endophytic microbes present in medicinal plants from both ecological and therapeutic point of view. In this review, we have studied different plant species found in North-East India showing the globe.
Plants from North-East India as a Source of Anticancer Phytochemicals

Plants have been using as source of food, shelter and medicine since the time of starting of human civilization.\textsuperscript{19} Dioscorides, one of the historically prominent Greek physician and pharmacologist in his 5 volume book “De Materia Medica,” described 600 medicinal plants used in different ailments.\textsuperscript{20} Herbal medicines are based on various cultural and traditional knowledge, hence, it is very well established way of searching novel phytochemicals for drug development based on traditional knowledge. Plant derived products has very less toxicity and much safer as compared to synthetic chemical drugs. Therefore, they are considered as the ideal candidate for modern drug discovery process. Different types of plant derived compounds and their metabolites are present in the root, stem, bark, leaves, and flower which serve diverse pharmacological activity in human healthcare. Compounds like alkaloids, flavonoids, Phenolics, glycosides, tannins, oils and gums are responsible for different therapeutic purposes. Till now, many phytochemicals such as taxol, topotecan, vinblastine and many more have been used successfully as anticancer drugs in clinical studies.\textsuperscript{21-23} Since North-East India is a great reservoir of plant resources, various types of bioactive secondary metabolites are produced by these plants which are used in different medicinal purposes including cancer. Table describes some plant species of North-Eastern India showing anticancer properties.

Importance of Endophytes as a Source of Cancer Drugs

Endophytes are a good source of anticancer activities that could have vital impact as an anticancer drug.\textsuperscript{24} Till date, many endophytes had been already reported that can produce bioactive compounds which are effective in anticancer assays.\textsuperscript{25} The first and famous anticancer drug, Taxol, was produced from the endophytic fungus \textit{Taxomyces andreanae} isolated from \textit{Taxus brevifolia} Nutt that produce good anticancer activity against the cancer cell lines\textsuperscript{26}. Figure 1 shows the recovering of fungal endophytes from plants and microscopic view of potent fungal endophyte. Several studies in recent times have been conducted where the taxol production by endophytes was boosted to maximum level via conjugation with gold nanoparticles which is then

Figure 1. A) Isolation of endophytic fungi from \textit{Cannabis sativus} and microscopic view of potent fungal endophyte \textit{Alternaria alternata}. B) Isolation of endophytic fungi from \textit{Capsicum annuum} and microscopic view of potent fungal endophyte \textit{Colletotrichum gleosporioides}
| No. | Name of the Plant | Part used | Types of cancer it works | Endophytes | Metabolites | Ref. |
|-----|-------------------|-----------|--------------------------|------------|-------------|-----|
| 1.  | Adenanthera pavonina L. | Bark, Seed | Leukemia, lymphoma, colon cancer | No data | Quercetin | 38 |
| 2.  | Ageratum conyzoides (L.) L. | Root, Leaves | Gastric carcinoma (SGC-7901), human colon adenocarcinoma (HT-29), leukemic, prostate cancer, breast cancer. | Shewanella spp., Pseudomonas spp. | 2-amino-3-quinoline, Oleic acid, 1,2-Benzenedicarboxylic acid, Phthalic acid | 39-43 |
| 3.  | Allium sativum L. | Bulb | Breast cancer, liver, colon, lung, cervix cancer, bladder carcinoma | Aspergillus terreus, Penicillium spp. | Allylmercaptocysteine, allicin | 44-47 |
| 4.  | Aloe vera (L.) Burm.f. | Whole plant | Liver cancer (HepG2), breast cancer (MCF-7), cervical cancer | NAF-1 strain endophytic actinobacteria | No data | 48-50 |
| 5.  | Alstonia scholaris (L.) R. Br. | Whole plant | Leukemia, Skin cancer Pancreatic cancer, Nasopharynx cancer | No data | No data | 51,52 |
| 6.  | Annona muricata L. | Leaves, Seed | Lung cancer (U937),leukaemia (HL-60, THP1), skin melanoma (B16), prostate cancer (PC-3) | Periconia spp. | Cigroisocoumarinol | 53 |
| 7.  | Azadirachta indica A. Juss. | Root | Breast, lung, liver, oral cavity, larynx Leukemia, Lung cancer | Fusarium tricinctum Nectria spp., Penicillium corylophilum, | 3-Hydroxypropionic acid, 3-Hydroxypropionic acid | 54-58 |
| 8.  | Bauhinia variegata L. | Leaf | Breast cancer | Bacillus spp. | Saponins, Alkaloids | 59,60 |
| 9.  | Betula pendula Roth. | Leaves | Leukemia, Lung cancer | Streptomyces spp. | Borneol, Camphor | 61-65 |
| 10. | Blumea balsamifera (L.) DC. | Leaves | Breast cancer, epidermal carcinoma of the mouth, myeloid leukaemia, lung cancer | Melanconium betulinum | 3-Hydroxypropionic acid, 3-Hydroxypropionic acid | 66-68 |
| 11. | Cajanus cajan (L.) Millsp. | Leaves | Breast cancer | Hypocrea lixii | Capsaicin | 66-68 |
| 12. | Camelia sinensis (L.) Kuntze | Leaves, Buds, Branches | Colorectal cancer | Pestalotiopsis fici | Siccayne [2-(3-Methyl-3-butene-1-ynyl) Hydroquinone] | 69-72 |
| 13. | Camptotheca acuminata Deane. | Whole plant | Colorectal cancer | Fusarium solani | Camptothecin | 73 |
| 14. | Cannabis sativa L. | Leaves | Breast cancer, brain/spine tumour, colorectal cancer, skin cancer | Alternaria spp., Penicillium spp., Rhizopus spp. | Cannabinoid | 74-77 |
| 15. | Capsicum annum L. | Whole plant | Various cancer types | Alternaria alternata | Capsaicin | 78 |
| 16. | Catharanthus roseus (L.) G. Don | Leaves | Nephroblastoma, acute lymphoblastic leukemia | Curvularia verruculosa | Vinblastine | 79 |
| 17. | Citrus medica L. | Root, Fruits, Leaves | Human lung carcinoma | Phyllosticta citricarpa | Taxol, Paclitaxel | 80-82 |
| 18. | Colchicum autumnale L. | Leaves Flower | Hepatocellular carcinoma | No data | Colchicine | 83,84 |
| 19. | Curcuma aromatica Salisb. | Rhizome | Breast cancer, leukaemia | Chaetomium globosum | Chaetoglobosin X | 82,85,86 |
| 20. | Daucus carota L. | Root | Leukaemia | Aspergillus ustus | Carotenoids, ascorbic acid, polyacetylenes | 80,87 |
| No. | Name of the Plant | Part used | Types of cancer it works | Endophytes | Metabolites | Ref. |
|-----|------------------|-----------|---------------------------|------------|-------------|-----|
| 21. | *Dillenia indica* Linn. | Stem, bark | Breast cancer | *Hypocrea* spp. | Betulinic acid | 88,89 |
| 22. | *Emlica officinalis* Gaertn. | Bulb | Various type of cancer | *Phomopsis* spp., *Xylaria* spp. | Quercitin, Gallic acid, Ellagic acid | 59, 90, 91 |
| 23. | *Enhydro Fluctuans* Lour. | Whole plant | Ehrlich's ascites carcinoma (EAC) | No data | Baicalein 7-O-glucoside, baicalein 7-O-diglucoside | 92,93 |
| 24. | *Fagopyrum esculentum* (Lehm.) Mansf. ex K.Hammer | Hull seed | Breast cancer, colon cancer | *Bionacteria pityroides*, *Fusarium oxysporum*, *Altemaria* spp. | Phenolic compounds like rutin | 94-96 |
| 25. | *Fragaria vesca* L. | Fruit | Hepatocellular carcinoma | No data | Borneol, Ellagic acid | 59, 97 |
| 26. | *Fritillaria* sp. | Whole plant | Inhibits proliferation and colony formation of cancer cells | *Fusarium* spp. | Peimine | 98 |
| 27. | *Glycyrrhiza glabra* L. | Root | Colorectal cancer, breast cancer | *Aspergillus* spp., *Chaetomium* spp., *Fusarium* solani | Glycyrrhizin, rutin, Cinnamic acid, Quercitin, Kaempferol, Taxol | 80, 99 |
| 28. | *Guayana esequiba* | Whole plant | Breast cancer, lung cancer, prostate gland cancer | *Seimatoantlerium tepuense* | No data | 100 |
| 29. | *Hevea brasiliensis* (Willd. Ex A.Juss.) Mull.Arg. | Whole plant | Breast cancer, lung cancer, skin cancer | *Eutypella scoparia* | Cytochalasins | 101 |
| 30. | *Huperzia serrata* (Thunb.) Trevis. | Whole plant | Various types of cancer | *Ceriporia lacerate* | Ceriponols | 102 |
| 31. | *Jatropha curcas* L. | Leaves, Seed, Root | Cervical cancer, colon cancer, lung cancer | *Collectotrichum truncatum*, *Nigrospora oryzae* | Gallic acid, rutin, Saponin Epicatechin, Kaempferol 3-O-β-glucoside, Kaempferol 3-O-α-rhamnoside, propanadin and rutin | 94, 103, 104, 105, 106 |
| 32. | *Litchi sinensis* Sonner | Leaves, Pericarp | Breast cancer, leukaemia, colorectal cancer | No data | | |
| 33. | *Maytenus hookeri* Loes. | Root nodules | Colon carcinoma | *Micromonospora lupine* | Lupinacardin | 107 |
| 34. | *Mentha pulegium* L. | Aerial parts | Gingival cancer, colon cancer, uterus cancer | *Stemphylium globuliferum* | Altersolanol | 108, 109 |
| 35. | *Mimosa pudica* L. | Whole plant | Leukaemia, lung cancer | No data | Flavonoids, mimosine | 110, 80 |
| 36. | *Mirabilis jalapa* L. | Bark, Leaves, Root | Breast cancer, cervical cancer | *Aspergillus clavatonicus* | Ribosome-inactivating protein (RIP) | 34, 111 |
| 37. | *Monarda citriodora* Cerv. Ex Lag. | Whole plant | Prostate cancer | *Fusarium oxysporum* | Paclitaxel | 112, 113 |
| 38. | *Nicotiana tabacum* L. | Leaves | Breast cancer | *Fusarium sambucinum* | Flavonoids like nicotelline, nicotianine, nicotine, Anatabine, Cotinine | 114, 80, 115 |
| No. | Name of the Plant | Part used | Types of cancer it works | Endophytes | Metabolites | Ref. |
|-----|------------------|-----------|--------------------------|------------|-------------|-----|
| 39. | Ocimum sanctum L. | Leaves    | Cervical cancer, Fibrosarcoma, Laryngeal epithelial sarcoma | Macrophomina phaseolina | Eugenol, carvacrol, methyl eugenol, carphyllene, flavonoids | 71, 116 |
| 40 | Panax ginseng C.A.Mey | Whole plant | Breast cancer | Paecilomyces spp. | Ginsenosides-Rg3, Rh2 | 117 |
| 41 | Piper nigrum L. | Leaves, Fruit | Colorectal cancer, Lung cancer | Colletotrichum gloeosporioides | Piperine | 118 |
| 42 | Pleurothallis immerse | Whole plant | Acute lymphoblastic leukemia | Fusarium spp., Plactosphaerella spp., Stemphyllum spp., Septora spp., Cladosporum spp. | Sitostenone, Tyrosol, L- asparaginase | 119, 120 |
| 43 | Podophyllum hexandrum Royle | Rhizome | Testicular gland cancer, Leukemia and solid tumors | Fusarium spp. | Podophyllotoxin | 121-124 |
| 44 | Potentilla fulgens var. macrophylla Cardot | Root | Leukemia, Lung cancer, Liver cancer | Curvularia clavata, Curvularia lunata, Fusarium oxysporum | Kaempferol (KMP), Ellagic acid (ELA) | 39, 125, 126 |
| 45 | Salacia oblonga Wall. | Whole plant | Disruption of microtubulin equilibrium | Alternaria spp., Fusarium solani | Taxol | 127 |
| 46 | Silybum marianum (L.) Gaertn. | Whole plant | Lymphoblastic Leukaemia, Breast cancer | Aspergillus izukae | Flavonolignans, Silibin A, Silibin B | 128 |
| 47 | Sinopodophyllum hexandrum (Royle) T.S.Ying | Whole plant | Hepatoma, Lung cancer, Neuroblastoma, Testicular cancer, | Pestalotiopsis adusta | Pestalustaine B | 129 |
| 48 | Smilax china L. | Rhizome | Colon cancer, Leukaemia, Prostate cancer | Mycosphaerella nawae | Isoflavone genistein, Quercitin, Baicalin, Kaempferol | 130, 131 |
| 49 | Solanum nigrum L. | Tuber | Breast cancer | SNFSt, SNFL and SNF | Salamargine | 132, 133 |
| 50 | Tarax baccata L. | Whole plant | Prostate gland cancer | Acremonium spp. | Leucinostatin A | 134-136 |
| 51 | Tarax wallichiana Zucc. | Inner bark | Breast cancer, Lung cancer, Prostate gland cancer | Seimatoantlerium nepalense | Taxol | 137 |
| 52 | Terminalia arjuna (Roxb. Ex. DC.) Wight & Am. | Stem, Bark | Colon cancer, Liver cancer, Prostate cancer, Ovarian cancer, | Chaetomella raphigera | Arjunic acid, Arjungenin, Arjunetin, Arjunoglucone | 138-140 |
| 53 | Tinospora cordifolia (Wild.) Miers | Leaves | Colon cancer, Cervical cancer, Oral squamous cancer, Ovary cancer | Cladosporium uredinica | 39, 141, 142 |
mediated by γ-irradiation\textsuperscript{27}. Similar studies on enhancement of anticancer activity by gamma irradiation using extracts of \textit{Aspergillus sydowii} isolated from the bark of \textit{Ricinus communis} are also observed.\textsuperscript{28} The endophytic fungi \textit{Leptosphaerulina australis}, \textit{Xylariaceae sp.}, and \textit{Stemphylium solanith} that were isolated from \textit{Morinda citrifolia} Linn. (Noni) inhibits the growth of human carcinoma cell lines MCF-7 (breast), LU-1 (lung), and PC-3 (prostate).\textsuperscript{29} \textit{Colletotrichum gloeosporioides} isolated from \textit{Barringtonia acutangula} was reported by Lakshmi et al. to shows anticancer activity against the Human Colon Cancer HT29 cell lines.\textsuperscript{30} The bioactive compound Eremofortin F isolated from the endophyte \textit{Diaporthe pseudomangiferae} showed cytotoxic activity on MRC5 cells and KB cells.\textsuperscript{31} The endophytic fungus \textit{Pestalotiopsis fici} showed strong cytotoxic activity against the mouse lymphoma cell line L5178Y.\textsuperscript{32} The endophytic fungi \textit{Alternaria} sp. isolated from \textit{Eremophila longifolia} showed cytotoxic activity against a lung cancer cell line and human broblast cell line.\textsuperscript{33} Cytotoxic activity was also shown by the endophytic fungi \textit{Penicillium} sp. isolated from \textit{Centella asiatica} against HeLa, A431, and human breast cancer (MCF7).\textsuperscript{34} All these studies reported by various researchers proved that endophytes are a very good source of anticancer drugs which can be used in various pharmaceutical industries. \textit{Penicillium oxalicum}, the endophytic fungi isolated from \textit{Amoora rohituka} was found to have anticancer activity. The breast cancer and T lymphoma cells was found to be inhibited by the ethyl acetate extract of \textit{P. oxalicum}.\textsuperscript{35} Several reports are also there where the cytotoxic and anticancer activities are observed by the endophytic bacteria. Species of \textit{Bacillus} as well as \textit{Micromonospora} isolated from \textit{Ibervillea sonorae} was found to have antitumor activities against L5178Y-R lymphoma cells.\textsuperscript{36} In addition to the plants, endophytes from liverworts also are reported to have anticancer properties. The endophytic extract from \textit{Marchantia polymorpha} was tested for anticancer activity and was found to be effective against a panel of cancer cell lines (FaDu, HeLa etc.).\textsuperscript{37}
CONCLUSION

Since time immemorial human beings are dependent on plant resources for fulfilling their various needs, medicines are one of the most essential parts of daily needs. Medicinal plants are a very rich source of various types of bioactive compounds, due to which they can show medicinal properties and can be used for remediation of different ailments. In developing countries, about 80% of the population especially from rural areas depends on herbal medicines for their health care needs (WHO report 2001). Different types of diseases cause suffering to different extent in human health. Cancer is one of the most serious health issues across the world, which takes millions of lives every year. The first time written record of human cancer was seen in ancient Egyptian manuscript. Though, cancer has afflicted human population since prehistoric time, but in recent few decades due to presence of increased amount of carcinogens in environment and in consumable products, prevalence of cancer is increasing day by day. In North-Eastern part of India also cancer has become a very common disease. Therefore, there is a very urgent need to search for potent plant bioactive metabolites for the effective treatment of cancer.

North East India is a biodiversity hotspot and inhabited by many tribal communities. These indigenous tribes use different medicinal plants for treating various diseases including cancer. Figure 2 shows structures of some of the major anticancerous compounds. But with the increasing population rapid commercialization demand for these plant derived products increases tremendously, which leads to biodiversity loss. Many plants have undergone destruction and are on the threat status. Therefore an alternative way of obtaining necessary bioactive compounds to combat with disease is very crucial. It is very fortunate that endophytic microbes have the capability to produce these metabolites. Therefore, they can be used as alternative source
for bioactive metabolites. In North-Eastern India till now very few endophytic studies are carried out, it is a very bright research approach for exploring the potentiality of endophytic microbes in synthesizing various metabolites. Therefore, we conclude that by extensive endophytic study we can save millions of people from deadly cancer without destroying biodiversity. In North-East India extensive endophytic study can open new doors for pharmaceutical companies which can make better human health.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

AUTHORS’ CONTRIBUTION
SK and AS conceptualised the idea, reviewed and prepared the draft manuscript. AH, SH, SPS and DK helped in reviewing, formatting and editing the manuscript. All authors read and approved the final manuscript for publication.

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DATA AVAILABILITY
All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT
Not applicable.

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