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MINI-REVIEW OPEN ACCESS

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

Sanjib Kalita[1], Anindita Sarma[1], Ankur Hazarika[2]*, Satarupa Hazarika[3], Saranga Pani Saikia[4] and Dibyajyoti Kalita[4]

[1]Department of Botany, Gauhati University, Guwahati - 781 014, Assam, India.
[2]Department of Zoology, Gauhati University, Guwahati - 781 014, Assam, India.
[3]Handique Girls' College, Guwahati - 781 001, Assam, India.
[4]Department 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

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INTRODUCTION

Cancer is one of the major challenges and is one of the leading causes of death globally. According to 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.[6] 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.[3,8] 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.[9-11]

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, swamps are characteristics in this region, which favors diversified species and wide range of vegetations from tropical to alpine forests.[12] 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.[13,14] 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.[15] 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.[16] Endophytes are quite common in vascular plants, and are present almost every vascular plant of this planet.[17] In 1866 De Barry for the first time coined the term endophytes.[18] 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.[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.[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.[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.[24] Till date, many endophytes had been already reported that can produce bioactive compounds which are effective in anticancer assays.[25] The first and famous anticancer drug, Taxol, was produced from the endophytic fungus *Taxomyces andreanae* isolated from *Taxus brevifolia* Nutt that produce good anticancer activity against the cancer cell lines[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

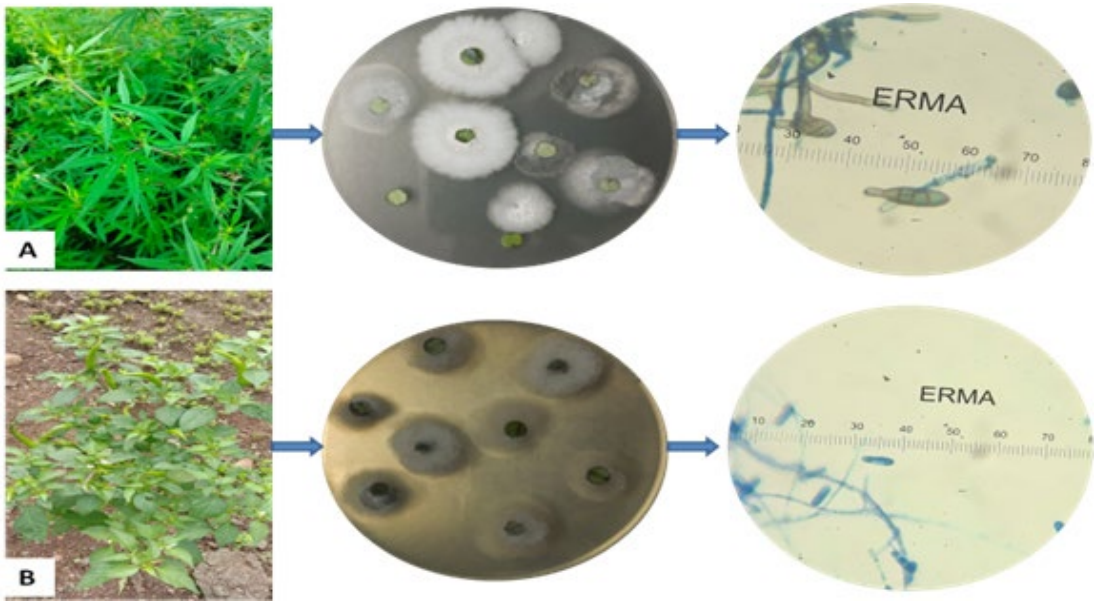

Figure 1. A) Isolation of endophytic fungi from *Cannabis sativus* and microscopic view of potent fungal endophyte *Alternaria alternata.* B) Isolation of endophytic fungi from *Capsicum annuum* and microscopic view of potent fungal endophyte *Colletotrichum gleosporioides*

Table. List of some plants having anticancer properties and associated endophytic microbes

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	Aloesaponarin	48-50
5.	*Alstonia scholaris* (L.) R. Br.	Whole plant	Leukemia, Skin cancer Pancreatic cancer,	No data	No data	51,52
6.	*Annona muricata* L.	Fruit	Nasopharynx cancer	*Perconia* spp.	Periconiasins	53
7.	*Azadirachta indica* A. Juss.	Leaves, Seed	Lung cancer (U937),leukaemia (HL-60, THP1), skin melanoma (B16), prostate cancer (PC-3)	*Fusarium tricinctum Nectria* spp., *Penicillium corylophilum*,	Citreoisocoumarinol	54-58
8.	*Bauhinia variegate* L.	Root	Breast, lung, liver, oral cavity, larynx	*Bacillus* spp.	Saponins, Alkaloids	59, 60
9.	*Betula pendula* Roth.	Leaf	Leukaemia, Lung cancer	*Melanconium betulinum*	3-Hydroxypropionic acid	61, 62
10.	*Blumea balsamifera* (L.) DC.	Leaves	Breast cancer, epidermal carcinoma of the mouth, myeloid leukaemia, lung cancer	*Streptomycetes* spp.	Borneol, Camphor	63 - 65
11.	*Cajanus cajan* (L.) Millsp.	Leaves	Breast cancer	*Hypocrea lixii*	Cajanol	66-68
12.	*Camelia sinensis* (L.) Kuntze	Leaves, Buds, Branches	Colorectal cancer	*Pestalotiopsis fici*	Siccayne [2-(3-Methyl-3- buten-1-ynyl) Hydroquinone]	69-72
13.	*Camptotheca acuminate* Decne.	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 ustas*	Carotenoids, ascorbic acid, polyacetylenes	80, 87

Table. Cont...

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.	*Emblica officinalis* Gaertn.	Bulb	Various type of cancer	*Phomopsis* spp., *Xylaria* spp.	Quercitin, Gallic acid, Ellagic acid	59, 90, 91
23.	*Enhydra Fluctuans* Lour.	Whole plant	Ehrlich's ascites carcinoma (EAC)	No data	Baicalein 7-O-glucoside, baicalein 7-O-diglucoside	92,93
24.	*Fagopyrum esculantum* (Lehm.) Mansf. ex K.Hammer	Hull seed	Breast cancer, colon cancer	*Bionacteria pityroides*, *Fusarium oxysporum*, *Alternaria* 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.	Peiminine	98
27.	*Glycyrrhiza glabra* L.	Root	Colorectal cancer, breast cancer	*Aspergillus* spp., *Chaetomium* spp., *Fusarium solani*	Glycyrrhizin, rutin, Cinnamic acid, Quercitin, Kaempherol	80, 99
28.	*Guayana esequiba*	Whole plant	Breast cancer, lung cancer, prostate gland cancer	*Seimatoantlerium* tepuiense	Taxol	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,	94, 103, 104 105, 106
32.	Litchi sinensis Sonner	Leaves, Pericarp	Breast cancer, leukaemia, colorectal cancer	No data	Kaempferol 3-O-β-glucoside, Kaempferol 3-O-α-rhamnoside, procyanidin and rutin	
33.	*Maytenus hookeri* Loes.	Root nodules	Colon carcinoma	*Micromonospora lupine*	Lupinacidin	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 clavatonanicus	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

Table. Cont...

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	Breat cancer	*Paecilomyces* spp.	Ginsenosides-Rg3, Rh2	117
41	*Piper nigrum* L.	Leaves, Fruit	Colorectal cancer, lung cancer	*Colletotrichum gloeosporioides*	Piperine	118
42	*Pleurothallis immerse* Linden & Rchb.f.	Whole plant	Acute lymphoblastic leukemia	*Fusarium* spp., *Plactosphaerella* spp., *Stemphylium* spp.,*Septoria* spp., *Cladosporium* spp.	Sitostenone, Tyrosol, L- asparginase	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	Leukaemia, 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, Silybin A, Silybin 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	Solamargine	132, 133
50	*Taxus baccata* L.	Whole plant	Prostate gland cancer	*Acremonium* spp.	Leucinostatin A	134-136
51	*Taxus wallichiana* Zucc.	Inner bark	Breast cancer, lung cancer, prostate gland cancer	*Seimatoantlerium nepalense*	Taxol	137
52	*Terminalia arjuna* (Roxb. Ex. DC.) Wight & Arn.	Stem, Bark	Colon cancer, liver canceroral cancer, ovarian cancer,	*Chaetomella raphigera*	Arjunic acid, Arjungenin, Arjunetin, arjunoglucoside	138-140
53	*Tinospora cordifolia* (Willd.) Miers	Leaves	Colon cancer, cervical cancer, oral squamous cancer, ocary cancer	*Cladosporium uredinicola*	N-formylannonain magniflorin, jatrorrhizine, palmitin, 11-hydroxymustakone, cordifolioside A, Tinocordiside, Yangambin	39, 141, 142

Table. Cont...

No.	Name of the Plant	Part used	Types of cancer it works	Endophytes	Metabolites	Ref.
54	*Vitex trifolia* L.	Leaf, Fruit	Leukaemia, Cervical cancer, breast cancer	*Pestalotiopsis fici*	Casticin, Trimethylquercetagetin	39, 143
55	*Withania somnifera* (L.) Dunal	Root	Human cervical cancer	*Alternaria* spp., *Cladosporium* spp., *Colletotrichum* spp., *Fusarium* spp., *Xylaria* spp.	5-Fluorouracil	144, 145
56	*Xanthium strumarium* L.	Root, Leaf, Fruit	Colon cancer, breast cancer, Lung cancer	*Paecilomyces* sp.	Xanthin, Xanthinocin, Xanthatin	34, 146
57	*Zingiber officinale* Roscoe	Rhizome	Breast cancer, colon cancer, Melanoma	*Aplosporella javeedi*	6-shogaol, Gigerol, Zingerone	147-149

mediated by ɣ-irradiation[27]. Similar studies on enhancement of anticancer activity by gamma irradiation using extracts of *Aspergillus sydowii* isolated from the bark of *Ricinus communis* are also observed.[28] The endophytic fungi *Leptosphaerulina australis,* Xylariaceae sp., and *Stemphylium solani*that were isolated from *Morinda citrifolia* Linn. (Noni)inhibits the growth of human carcinoma cell linesMCF-7 (breast), LU-1 (lung), and PC-3 (prostate).[29] *Colletotrichum gloeosporioides* isolated from *Barringtonia acutangula*was reported by Lakshmi et.al. to shows anticancer activity against the Human Colon Cancer HT29 cell lines.[30] The bioactive compound Eremofortin F isolated from the endophyte *Diaporthe pseudomangiferae* showed cytotoxic activity on MRC5 cells and KB cells.[31] The endophytic fungus *Pestalotiopsis clavispora* that was isolated from *Rhizophora harrisonii* produce the compound pestalpolyol that showed strong cytotoxic activity against the mouse lymphoma cell line L5178Y.[32] The endophytic fungi *Alternaria sp.* isolated from *Eremophila longifolia* showed cytotoxic activityagainst a lung cancer cell line and human broblast cell line.[33] Cytotoxic activity was also shown by the endophytic fungi *Penicillium sp.* isolated from *Centella asiatica* against HeLa, A431, and human breast cancer (MCF7).[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. *Penicillium oxalicum*, the endophytic fungi isolated from *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 *P.oxalicum.*[35] Several reports are also there where the cytotoxic and anticancer activities are observed by the endophytic bacteria. Species of *Bacillus* as well as *Micromonospora* isolated from *Ibervillea sonorae* was found to have antitumor activities against L5178Y-R lymphoma cells.[36] In addition to the plants, endophytes from liverworts also are reported to have anticancer properties. The endophytic extract from *Marchantia polymorpha* was tested for anticancer activity and was found to be effective against a panel of cancer cell lines (FaDu, HeLa etc.).[37]

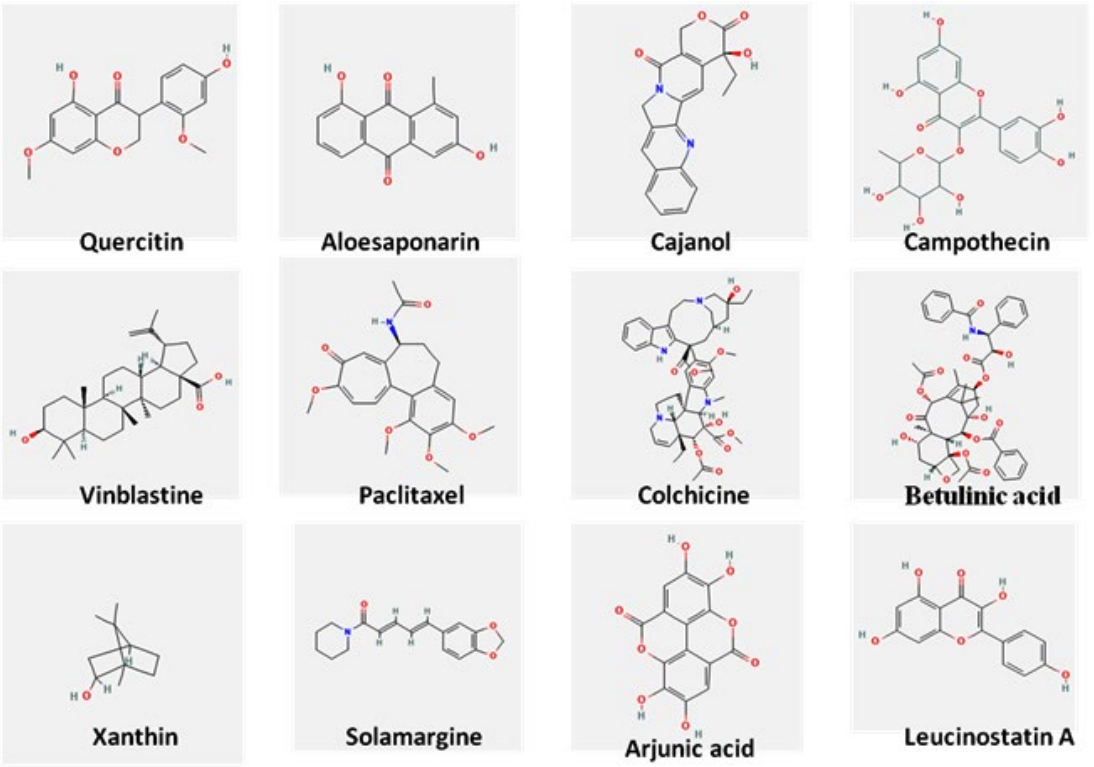

Figure 2. Chemical structure of some major anticancerous compounds (SOURCE: Pubchem)

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.[150] 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 anticancer 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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