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Review

Exploring the Chemopreventive Potential and Ethnobotanical Use of Medicinal Plants Available in the Northeast Region of India

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Abstract

Northeast India is a repository of rich plant resources and traditional knowledge of medicinal plants. These plants are in use by different ethnic groups of the region for various ailments and diseases. This paper reviews the ethnobotanical and therapeutic applications of medicinal plants known to various ethnic group in Northeast India that have been passed down through generations. It identifies the key bioactive compounds from the plants responsible for anticancer activities, making them potential chemopreventive agents. Furthermore, the paper also underlines the synergistic effects of these plants when combined with chemotherapeutic drugs. Thus, shedding light on combinatorial approach that can aim to enhance the effectiveness of cancer treatment.

Keywords: Chemoprevention; Anticancer; Phytochemical; Northeast India; Bioactive compound; Medicinal plant

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Introduction

Cancer or malignant tumors which is characterized by abnormal growth and proliferation of cells, is the second most prevalent cause of mortality worldwide after cardiovascular diseases. The World Health Organization (WHO) predicts that there are 18.1 million cancer patients globally and that the disease will be responsible for 10 million deaths in 2020 [1]. It is predicted that there would be 17 million cancer deaths annually and 26 million additional cases of cancer by 2030 [2]. Global cancer patterns show significant geographic variations, with high-income countries generally experiencing higher incidence rates, but better survival outcomes compared to low- and middle-income countries [3]. Lung cancer continues to be the leading cause of cancer deaths globally, accounting for approximately 1.8 million deaths annually [4]. However, breast cancer has surpassed lung cancer as the most diagnosed cancer worldwide, with 2.3 million new cases per year [5]. Recent epidemiological trends show concerning increases in colorectal cancer among younger adults under 50, prompting revised screening guidelines in many countries [6]. Cancer cases are low in India as reported by WHO 2020 that documented 1.32 million new cancer diagnoses, substantially fewer than the 2.28 million cases reported in the United States. However, despite this lower incidence, India experienced approximately 850,000 cancer-related deaths, exceeding the United States' 610,000 deaths by about 30% [7,8]. The rise of cancer cases at an alarming rate are due to many factors such as migration of people from rural to urban areas, changes in their dietary habits, changes in lifestyle etc. [9,10].

Cancer can initiate in any part of the body by transformation of normal cells into malignant form. This transformation occurs in a multistage process where a person's genetic factors interact with many physical, chemical, and biological environmental factors (e.g. UV radiation, tobacco, virus, bacteria etc.). As a result of such interactions, mutation arises in cells leading to abnormal cell division which ultimately leads to tumor formation having the ability to invade other parts of the body [11]. Chemical compounds having the ability to control the occurrence of disease by pharmacological intervention are known as chemopreventive agents. Many chemopreventive agents in the form of anticancer drugs are present today, several of which are under clinical trials. Chemotherapy is the most effective way to treat cancer where various conventional drugs (e.g. Cisplatin, doxorubicin) are used. Unfortunately, therapeutic efficacy of these drugs is compromised due to development of adverse effects in the host normal cells/ tissues and acquired drug resistance [12]. Despite considerable efforts made to improve health care facilities, the burden of cancer continues to grow due to tremendous financial strain of high cost and poor accessibility of the synthetic chemotherapeutic medicines. Many researches and investigations are underway to find suitable medication and cure for cancer but a perfect cure remains elusive. In this regard plant and plant-derived compounds would be a promising source of anticancer pharmaceuticals. Therefore, there is a constant demand to search for anticancer compounds from plants which would play a critical role in development of drugs that would be safe, effective, and affordable [13]. The northeast India comprises half of the India's biodiversity and is home to many traditional herbal medicines. There are several potent bioactive compounds isolated from medicinal plants available in North-East India that are responsible for their anticancer and chemopreventive activity. The purpose of the study is to review and document the ethnobotanical and therapeutic applications of medicinal plants used traditionally by various ethnic groups in Northeast India, with a specific focus on their potential anticancer properties.

Methods

The study employs ethnobotanical surveys and interviews with traditional healers, village elders, and community members across Northeast Indian ethnic groups to document indigenous knowledge of medicinal plants used for cancer and related conditions. It also involves systematic literature review of published ethnobotanical studies, traditional medicine texts, and scientific research on Northeast Indian medicinal plants with potential anticancer properties.

Botanical diversity in Northeast India

The North Eastern Region of India is situated between 22°N and 29°5'N latitude and 88°00'E and 97°30'E longitudes. This region of India includes the state of Assam, Arunachal Pradesh, Meghalaya, Manipur, Mizoram, Nagaland, Sikkim, and Tripura is one of the nine global biodiversity hotspots. This biogeographic region is the richest reservoir of plant resources due to diverse topography and optimal climatic condition. 50% of India's flora is supported by this region which comprises of orchids, bamboos, ferns, zingibers, rhododendrons and many other medicinal plants as well as endemic species [14,15]. Northeast India is home to over 200 angiosperm families, many of which are economically and medicinally significant. The Northeast region of India is renowned for its highly humid climate, high rainfall, and moderate temperature which is responsible for the region's lowland and montane tropical evergreen woods ranging from moist to wet. It spans 8% of the country's geographical region of coverage out of which 75% is recorded as forest area. Much of the forest cover are due to 4 states: Mizoram, Manipur, Nagaland, and Meghalaya [16]. The varied forest and vegetation types from grasslands, swamps marshes to mixed deciduous and humid evergreen forests, as well as alpine and temperate vegetations are found here. This region is also inhabited by many distinct tribes with diverse culture and customs revolving around indigenous traditional knowledge system on plant-based medicine. North

east India is inhabited by 200 important tribes out of 450 tribes in the country, of different ethnic group and different cultural entities. They have intense knowledge about the plants around them and how these plants and their products can be used for curing various ailments. These tribes having immense faith in their traditional knowledge system mainly depend on herbal medicines to fulfill their healthcare needs. The region's unique physiography facilitates the growth of numerous medicinal plants that are utilized by the various ethnic groups of that region for basic healthcare purposes [17]. The different biogeographic zones of northeast India harbors many different medicinal plant species such as *Andrographis paniculata, Bacopa monnieri, Berberis aristata, Coptis teeta, Curcuma* spp., *Illicium griffithii, Ocimum sanctum, Oroxylum indicum, Piper longum, Rauwolfia serpentina, Taxus wallichiana, Terminalia arjuna, T. chebula, Tinospora cordifolia, Valeriana jatamansi,* and *Zingiber officinale* which are being used to produce crude drugs that are being traded in the national and international markets [18].

Ethnobotanical uses of the medicinal plants

From the beginning of human civilization, plants have been used as the source of food, shelter, fodder, and medicines. Medicinal plants hold a fundamental part in improvement of human civilization because many advanced drugs are created by using plants. Since ancient times medicinal needs have been fulfilled by herbal formulations prepared with the help of traditional knowledge such as Ayurveda, Kampo, Egyptian medicine and traditional Chinese medicine [17,19]. As discussed earlier, tribal population in northeast region of India is higher than any other areas of the country and each tribe have their own conventional wellness practices. Here are some ethnobotanical reports on some important medicinal plants used by the tribal people for treatment of different diseases and ailments (Table 1).

Bioactive compounds with chemopreventive properties found in plants of North East India

Treatment of cancer with synthetic drugs possesses a major challenge because it comes with various limitations such as severe toxicity, drug resistance, poor outcomes, and a high risk of relapse. As mentioned earlier, there is an urgent need to find a better and safer alternative for cancer treatment by screening of various phytochemicals from natural sources. As of now many phytochemicals such as Taxol, vinblastine, paclitaxel, and many more have been identified as successful anticancer drugs [63]. Table 2 discusses some plants from Northeast India with pharmacologically active compounds showing anticancer properties.

The underlying mechanism of chemoprevention for the bioactive compounds

With cancer cases rising at an alarming rate in today's world, understanding the molecular mechanism behind diverse cancers can aid in developing novel anticancer drugs. Several phytochemicals with known anticancer activity can inhibit cell proliferation, suppress migration/ invasion induce, promote apoptosis, and inhibit cell cycle arrest. Phytochemicals such as resveratrol, quercetin, kaempferol, vincristine, vinblastine, and podophyllotoxin serve as vital drugs having chemopreventive properties. These phytochemicals often act via modulating gene expression related to various molecular pathways implicated in growth and progression of cancer such as preventing uncontrollably rapid cell division, promoting apoptosis, and regulating the immune system.

General mechanism of action

Phytochemicals can inhibit cancer through their interactions with transcription factors, receptors, protein channels, immune cells, protein channels, pumps, oncogenic and tumor suppressor proteins. Plant-derived bioactive compounds in combination with cancer chemotherapeutics have been shown to exert their anticancer effects through the regulation of different signaling pathways. In this section we will discuss the pharmacologic action and molecular or specific targets of some bioactive anticancer compounds derived from plants available in the northeast region of India. Different mechanisms through which phytochemical compounds confer their anticancer activity include modulating cellular pathways, DNA damage, initiation of apoptosis, preventing the formation of carcinogenic species and cell cycle arrest. Disruption of cellular processes such as cell cycle arrest, angiogenesis, autophagy, reduction of oxidative stress, metastasis etc. are the result of signaling molecules and their interactions with various factors of signaling pathways. These factors that aid in chemoprevention by phytochemicals are transcription factors, tumor suppressor proteins, kinases, cyclins, and microRNA.

Key Signaling Pathways in Cancer Chemoprevention

Signaling pathways governing cell growth and survival are Mitogen activated protein kinase (MAPK), Janus activated kinase (JAK)/ signal transducer and activator of transcription protein (STAT), and nuclear factor Kappa B (NF-κB). These pathways are either hyperactivated or dysregulated, affecting the metabolism of several cancer cell types leading to metastasis, prolonged angiogenesis, proliferation, and dedifferentiation [127]. The PI3K-AKT signaling pathway supervises cell division as well as apoptosis which is predominantly hyperactivated in cancer cells [128]. Phytochemicals are reported to block histone deacetylase's role in increasing the transcription of genes like p21, Bax, and BAD promoting apoptosis. They can also inhibit the PI3K-AKT signaling in cancer cells, which results in decreased PTEN expression and reduced phosphorylation of AKT [128].

Curcumin from Curcuma longa

The phenolic compound of *Curcuma longa* L.- Cur-

Table 1. List of medicinal plants used by the people of northeast India

Scientific name of the medicinal plant	Local name (Northeastern state)	Part(s) used	Ethnobotanical use	References
Aegle marmelos	Sempri (Meghalaya) Heiri- khagok (Manipur) Bael (Tripura)	Fruit, Leaves, Bark	Mature fruit treats dysentery and diarrhea; ripe fruit aids heart health as tonic and laxative. Leaves with Cajanus Cajan used for jaundice.	[20,21]
Abelmoschus manihot	Usipak (Assam)	Flowers	Used for kidney disease, bronchitis, and toothache	[17,22]
Acorus calamus	Kiile tolyo (Arunachal Pradesh) Bajao (Sikkim)	Rhizome	Rhizome paste treats headache, wounds, rashes, and joint pain; also used for fever, epilepsy, diarrhea, sore throat, and asthma.	[23,24]
Amaranthus spinosus	Hatikhutora (Assam)	Stems and roots	Treats gonorrhea, menorrhagia, and snakebite	[25]
Alstonia scholaris	Sokson (Meghalaya)	Leaves, Bark	Treats fever, epilepsy and respiratory diseases.	[26]
Anemone rivularis	Bat soh plia (Meghalaya)	Leaves	Crushed leaves inhaled to cure sinusitis.	[27]
Annona squamosa	Aathe fal (Assam)	Roots and Leaves	The decoction prepared from roots and leaves is consumed orally three times to eliminate mosquito larvae; additionally, the smoke is utilized and the plant is cultivated near residential areas.	[165]
Adhatoda zeylanica	Bahak tita (Assam)	Leaves	Cough, glandular tumors, diarrhea and dysentery.	[28]
Ageratum conyzoides	Paas pai (Arunachal Pradesh)	Leaves	Applied to cut and wounds.	[29]
Allium cepa	Pyaz	Inflorescence or whole plant	Cold, cough and skin rashes	[166]
Aphanamixis polystachya	Heirangkhoi (Manipur)	Fruit	liver diseases, enlarged spleen, tumor, and abdominal complains.	[30]
Aconitum heterophyllum	Bikh, Paunkar (Sikkim)	Roots	Treats cold, cough and fever; also used as pain killer.	[31]
Angelica archangelica	Khomog (Sikkim)	Roots	Treats epilepsy, skin itching, and ulcers.	[32]
Andrographis paniculata	Boner kalomegh (Tripura) Hnahkhapui (Mizoram) Vubati (Manipur) Chiraitateeta (Arunachal Pradesh)		Treats Ulcerative colitis, Diarrhea, Dysentery, Jaundice, Malarial Fever, Rheumatism and Stomachache.	[33,34,35,36]
Asparagus racemosus	Satamul (Assam)	Roots	Treats intestinal helminths.	[37]
Artocarpus gomezianus	Khorika-dewa (Assam) Armu	Fruit, Bark	Headache, dizziness	[38]
Bauhinia variegata	Megong (Meghalaya)	Leaves	Reduces blood pressure; flowers are eaten to treat piles and dysentery.	[39,40]
Bryophyllum pinnatum	Dupartenga (Assam)	Leaves	Used for wound healing, snakebite, bruises, boils, jaundice, dysentery, urinary trouble	[41]
Baccaurea ramiflora	Moktok hei (Manipur) Leteku (Assam)	Fruit, Bark	Bark is used as medicine for constipation.	[42]
Bacopa monnieri	Leibak kundo macha (Manipur)	Leaves, stem	Memory tonic, treats anxiety, epilepsy, enhances learning.	[43]
Centella asiatica	Thunmankuni (Tripura) Bor manimuni (Assam) Thunmankuni (Manipur)	Whole plant	Used for dysentery; juice serves as mouthwash.	[39,45]
Coptis teeta	Mismi Teeta (arunachal Pradesh)	Leaves	Treats decreased vision, inflammation in eye diseases, cataract, skin-related problems, indigestion, constipation, malarial fever, gonorrhea, jaundice, and urine disorders.	[46]
Crypteronia paniculata	Mosuginsep (Meghalaya)	Leaves and bark	Used to treat Snake bite and wound	[44]
Cynodon dactylon	Doob pataa (Tripura) Tingthou (Manipur)	Leaves/ whole plant	Used for rheumatic swellings; stops bleeding; leaf mixture treats thyroid.	[47,48]

Dillenia indica	Tedike (Meghalaya) ou tenga (Assam)	Fruit	Treats wounds and burns, stomach disorders, cure dandruff and hair fall problem.	[49]
Elaegnus umbellate	Heiyai (Manipur)	Fruit, seed	Fruit is used to improve digestion; seeds are consumed to cure cough	[42]
Euphorbia nerifolia	Euphorbia nerifolia / Sairapal (Tripura)	Leaves	Leaf juice is used to treat ear infection and its vapors are inhaled during fever.	[50]
Garcinia pedunculata	Heibung (Manipur) Bor-thekera (Assam)	Leaves and fruit	Used to treat dysentery, diarrhea, and stomach disorders.	[44]
Gynostemma pedata	Riikoh (Arunachal Pradesh)	Tuber and stem	Stem and tuber powder treats cough, throat pain and stomach ailments.	[44]
Gardinia companulata	Lam-Heibi (Manipur)	Leaves	Used to treat boils and for diabetes.	[42]
Houttuynia cordata	Ja-myrda (Meghalaya) Siyan hamang (Arunachal Pradesh) Nuichua (Nagaland)	Leaves	Treats sprains, stomach ulcers, anemia, tuberculosis, and worm infections.	[51]
Hydrocotyle rotundifolia	Horu manimuni	Whole plant/ leaves	Treats colds, pneumonia, stomach issues, liver problems, nerve disorders; induces appetite; purifies blood; improves skin conditions.	[44]
Jatropha curcas	Girogaachh (Tripura)	Branches	Sap treats gum infections; lowers blood pressure.	[50]
Leucas aspera	Doron pushpa (Tripura)	Leaves	Leaf extract treats cough and jaundice; eaten for pain, digestive and joint issues.	[44]
Litsea cubeba	Ngairong (Manipur) Tayer (Arunachal Pradesh)	Fruit	Used as condiment or spices in Curries, chutney and pickle.	[52]
Lagerstroemia speciosa	Asari (Meghalaya)	Bark, root	Used to treat jaundice and dysentery.	[44]
Michelia champaca	Salyo sanii (Arunachal Pradesh)	Bark and seeds	Seeds eaten as appetizers and used for stomach and gastric problems.	[44,53]
Mimosa pudica	Dugjat lajar (Tripura) Lajuki lata (Assam)	Leaves	Root juice used for urinary disorders; Leaf juice with milk used for piles.	[44,45]
Melia azedarach	Dieng-jah-rasang (Meghalaya)	Leaves	Used to treat skin infection, mouth and foot disease of livestock.	[54]
Momordica charantia	Tita kerela (Assam)	Leaves/fruits/ seeds	used for diabetes treatment.	[55]
Ocimum sanctum	Lapane (Assam)	Leaves	Leaf extract used to treat stomach and head ache.	[56]
Olea ferruginea	Chorphon (Manipur)	Leaves, fruit	Leaves used to treat piles and fruit is used as digestive [33].	[42]
Oxalis corniculata	O- khui hamang (Arunachal Pradesh) Ching-yensil (Manipur)	Leaves	Leaf paste is applied to wounds, used for bad breath, and joint pain.	[44,48]
Oroxylum indicum	Totola, Shivnak (Sikkim) Shamba (Manipur)	Bark, Leaves	Bark treats bladder issues, kidney stones, diarrhea, and anorexia; decoction with herbs used for tonsillitis, sore throat, and sinus.	[44,48]
Paederia foetida	Epitari (Arunachal Pradesh) Bhedailata (Assam)	Leaves	Crushed leaf juice for dysentery; leaf extract with salt for abdominal pain.	[57,58]
Psidium guajava	Sapri (Tripura)	Young shoot	Young twigs chewed for diarrhea, dysentery, and piles; fruit used for anemia	[45]
Solanum kurzii	Soh ngang rit (Meghalaya)	Fruit	The fruit is used as anti-allergy treatment.	[59]
Saccharum officinarum	Saccharum officinarum (Manipur)	Stem/ fruit	Juice is drank every day to cure jaundice.	[48]
Spilanthes paniculata	Ansha (Tripura) Marsang Byadhi or Marcha, Yakhohama (Arunachal Pradesh)	Leaves, Flowers, and young stem	Boiled leaves with rice for stomach issues; also for toothache, body ache, cough, fever, worms, liver trouble, constipation. Crushed flowers for dental problems.	[44,60,56]
Terminalia chebula	Manahi (Manipur) Bukhala buthai (Tripura)	Fruit	Used as anti-inflammatory, mild purgative; treats cough, cold, piles, ulcers, stomach ache, and jaundice	[42,45]
Xanthium strumarium	Ogaro (Assam)	Roots/Leaves	leaf decoction used orally to treat malaria.	[61]
Zanthoxylum acanthopodium	Mukthrubi (Manipur)	Seeds	Seed powder mixed with water is taken to treat gas formation.	[48]

Table 2. Phytochemicals with chemopreventive properties derived from plants available in Northeast India

Medicinal Plant	Bioactive compound	Study design (animal/ cell line)	Concentration/ Doses	Outcome/ mechanism of action	References
Acorus calamus	alpha (α)-and beta (β)-asarone	Human glioblastoma U251.	360 and 480 μM	β-asarone significantly inhibited the cell viability of human glioblastoma U251 cells.	[64,65]
Aegle marmelos	Citronellol and Auraptene	MDA-MB-231; A2780 and Hela cell lines	10-100 μM	CT induces apoptosis in MCF-7 human mammary tumor cells. Auraptene reduced A2780 cell viability and suppressed MMP-2 enzymatic activity	[66,67]
Artocarpus gomezianus	Cycloartobiloxanthone	Human lung cancer cell lines (H460, H23, A549 and H292).	0-100 μM	Apoptotic cell death was the main mechanism of toxicity of cycloartobiloxanthone.	[68]
Annona squamosa	Bullatacin	KB cells	_	The active fraction isolated from *Annona squamosa* seed extracts have strong antitumor activities which is shown by apoptosis inducing capacity.	[69]
Allium cepa	Quercetin	Thyroid cancer cells (TPC-1, BCPAP, HTori-3, SW480, and BT-20 cells)	1, 10, and 50 μM	Quercetin induced apoptosis by inducing only pro-NAG-1 expression, NAG-1 may serve as a novel biomarker for thyroid cancer prognosis	[70]
Bryophyllum pinnatum	Bryophyllin A	HeLa cells	50, 100, 250,500 and 750 μg/mL	Downregulated constitutively active AP1 specific DNA binding activity and suppressed oncogenic c-Fos and c-Jun expression which was accompanied by inhibition of HPV18 transcription.	[71]
Bauhinia variegata	Kaempferol	MCF-7 breast cancer cells; human bladder cancer EJ cells; colon cancer cell lines: RKO and HCT-116,	50–100 μM	Kaempferol inhibited bladder cancer invasion and metastasis; alters the cells at the molecular level.	[72-76]
Blumea balsamifera	Quercetin	Human hepatocellular carcinoma cells (McA-RH7777, HepG2)	12.5, 25 and 50 μg/mL	BME induced G1 cell cycle arrest by reducing cyclin-E and Rb phosphorylation in a dose- and time-dependent manner.	[77,78]
Catharanthus roseus	Vinblastine, vincristine	Breast cancer (MCF-7)	0.2-1.2 μM	temporary low-dose treatment with VBT and VCT increased PAI-1 release from MCF-7 cells	[79]
Clerodendrum viscosum	Catechin, Tannic acid, Reserpine and Rutin	Breast Carcinoma (MCF-7)	0-300 μg/mL	The FACS-based cell cycle analysis showed increased subG1 (apoptosis) population dose dependently.	[80]
Coptis teeta	Berberine	MCF-7 (breast cancer), HT29 (colon cancer), Tca8113 (oral squamous cell carcinoma), CNE2 (nasopharyngeal carcinoma cell), and Hela (cervical carcinoma).	47-12000 μM	Berberine exhibited cytotoxic effects on multiple cancer cell lines by inducing apoptosis and cell cycle arrest.	[81]

Curcuma spp. (C. angustifolia, Curcuma longa, C. caesia, C. amada, C. aromatica, C. aeruginosa)	Diferuloylmethane, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione or Curcumin	Highly metastatic breast cancer cell line (MDAMB-231).	0.5-30 µg/mL	Dose-dependent inhibition of cell growth, increases Bax, decreases Bcl-2, suppresses cell migration, and downregulates Rac-1 and MMP-9 expression/activity.	[82]
Cannabis sativa	Cannabinoid	Acute monocytic leukemia cell line, the THP-1.	0-100 µM	Correlation between p53 expression and CBG or CBN doses suggesting potential activation of p53-associated signaling pathways	[83]
Centella asiatica	Asiatic acid	Nasopharyngeal Carcinoma Cells (cis NPC-039 and cis NPC-BM); human SK-MEL-2 melanoma cells; HepG2 human hepatoma cells.	0, 25, 50, 75 µM	AA-induced apoptotic pathway through the phosphorylation p38 in human cisplatin-resistant nasopharyngeal carcinoma; also decreased viability and induced apoptosis of HepG2 human hepatoma cells	[84-86]
Dendrobium nobile	Dendrobine Erianin	A549 lung cancer cells; nasopharyngeal cancer cell lines (NPC-039 and NPC-BM cells).	10,1, and 10 µM,	Dendrobine induced apoptotic cell death through mitochondrial-mediated pathway; Erianin significantly increased activation of apoptosis in NPC cell lines and arrest the cell cycle	[87,88]
Dioscorea bulbifera	Diosbulbin C	non-small cell lung cancer (A549 and NCI-H1299 cells).	100 and 200 µM	Diosbulbin C treatment in NSCLC cells results in reduction in cell proliferation and induces significant G0/G1 phase cell cycle arrest.	[89]
Dillenia indica	Betulinic acid (BA) koetjapic acid (KA)	human leukemic cell lines (U937, HL60 and K562); oral squamous cell carcinoma (OSCC).	10-100 µM	BA and KA imparts cytotoxicity and induce apoptosis in OSCC cell lines	[90,91]
Dendrobium chrysotoxum	Erianin	Triple-negative breast cancer (TNBC)-MDA-MB-231 and EFM-192A.	10-320 nM	Erianin arrests G2/M phase, activates apoptotic pathways, and inhibits PI3K/Akt signaling.	[92]
Eclipta alba	Luteolin	breast cancer cell line (MCF-7).	50–200 µg/m	CFEA triggers intrinsic apoptosis by disrupting mitochondrial potential, increasing Hsp60, and downregulating XIAP.	[93]
Euphorbia hirta	2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one (DDMP)	colon cancer cells (SW620 and HCT116).	0-1.5 mg/mL	Treatment with different DDMP concentrations for various periods inhibited the growth of colon cancer cells followed by the induction of apoptosis in a dose dependent manner.	[94]
Ficus hispida	Hispidin	Colon cancer cells (HT-29).	0-200 µg/mL	Hispidin induced apoptosis through up-regulation of both intrinsic and extrinsic apoptotic pathways.	[95]
Flacourtia jangomas	β-sitosterol	hepatocellular cells (Huh7 and HepG2).	40, 20, 10, 5, 2.5, 1.25 µg/mL	β-S and β-SG exhibited cytotoxic activities via inducing apoptosis and activating caspase-3 and -9 in these cells.	[96]
Garcinia pedunculata	Garcinol	Prostate cancer cell lines (PC3, C4-2B and LNCaP); Pancreatic cancer cell (BxPC-3 and Panc-1).	5-25 µM	Garcinol effectively induces apoptosis in prostate cancer cells. It inhibits proliferation and induces apoptosis in pancreatic cancer cells	[97,98]

Glycosmis arborea	Skimmianine	Esophageal squamous cell carcinoma (ESCC)-TE-1 and Eca109 cells; xenografted Eca109 tumors in nude mice	0, 25, 50, 100 μM	SK inhibited TE-1 and Eca109 cell proliferation by inducing G0/G1 arrest and blocked migration and invasion by regulating EMT in vitro. It also suppressed the growth of xenografted Eca109 tumors in nude mice.	[99,100]
Gmelina arborea	Verbascoside	Glioblastoma cells (U87 cells); xenograft mouse model.	5 mg or 10 mg per mouse	VB reduced glioblastoma cell proliferation, migration, invasion, and increased apoptosis; VB also suppressed tumor growth in a xenograft model.	[101]
Hibiscus sabdariffa	Protocatechuic acid (PCA)	Human gastric carcinoma (AGS cells); Human Lung Cancer (A549). B16/F10 melanoma cells injected in mice (metastasis model in vivo)	0, 0.1, 0.5, 1.0 and 2.0 mM	PCA inhibited migration and invasion at non-cytotoxic doses. PCA also reduced liver metastasis of B16/F10 melanoma cells in mice	[102,103]
Houttuynia cordata	2-undecanone	lung adenocarcinoma (B[a]P) stimulated in animal model.	100 and 200 mg/kg	*H. cordata* and 2-undecanone significantly suppressed B[a]P-induced lung tumorigenesis without causing obvious systemic toxicity in mice.	[104]
Heliotropium indicum	Pyrrolizidine Alkaloids (Heliotrine, lasiocarpine)	cervical cancer cell line (HeLa).	200-100 μg/mL	The methanolic extracts of leaf and stem of *H. indicum* exhibits cytotoxic activity.	[105]
Illicium griffithii	6-allyl-6-(3-methylbut-2-en-1-yl) benzo[d] dioxol-5(6H)-one	pancreatic cancer (MIAPaCa2) and lung cancer (A549) cell lines.	20 μg/mL	6-allyl-6-(3-methylbut-2-en-1-yl)benzo[d][1,3]dioxol-5(6H)-one (1) exhibited significant cytotoxicity activity against Lung cancer (A549) and pancreatic cancer (MIAPaCa2) cell lines	[106]
Jatropha curcas	Curcusone C and D	Human cervix carcinoma cells (HeLa) and mouse lymphoma cells (L5178y).	0.1; 0.3; 1.0; 3.0, and 10.0 μg/mL	The pure diterpenoids showed strong cytotoxic activity.	[107]
Lagerstroemia speciosa	Corosolic acid Quercetin	human colon cancer cells (HCT116)	10-30 μM	CA induces caspase-dependent apoptosis by upregulating Bax/Fas/FasL and downregulating Bcl-2/survivin.	[108,109]
Litsea cubeba	1,8-cineol and citral	Human colon cancer cell lines (HCT116 and RKO); RKO cells injected into the SCID mice; Breast cancer cell lines (MCF 7 and MDA MB 231); prostate cancer cells (PC-3 and PC3M).	5, 10, 12.5 and 25 mM	1, 8-cineole induced apoptosis in human colon cancer cell lines HCT116 and RKO. In Xeno transplanted SCID mice it inhibited tumor progression; Curcumin and citral synergistically induced apoptosis and G0/G1 arrest in breast cancer cells without affecting normal cells.	[110-112]
Michelia champaca	Camphorsulfonic acid, Octadecadienoic acid	The human breast adenocarcinoma (MCF-7).	_	*M. champaca* seed and flower extract were effective against MCF-7 cells	[113]

Mimosa pudica	Myricetin	Human erythroleukemic cell line (K562) and human lung adenocarcinoma cell line (A549); Dalton's Ascites Lymphoma (DAL) injected into Swiss albino mice.	1-300 µg/mL (*in vitro*)25 mg/kg and 100 mg/kg body weight (*in vivo*)	The compound isolated has shown potent anticancer activity against tumor cell lines; A549 and K562. The histology revealed that the compound could protect the cellular architecture of liver and kidney of the mice.	[114]
Nardostachys jatamansi	Lupeol and β-sitosterol	Breast carcinoma (MDA-MB-231 and MCF-7).	20 µg/mL (NJM and NJDE)and 35 µg/mL (NJPE and NJEA)	NJM, NJPE and NJEA caused G2/M arrest while NJDE caused G0/G1 phase arrest in MDA-MB-231 cells. Further, NJM/fractions induced cell death by apoptosis	[115]
Oroxylum indicum	Chrysin, biochanin A and baicalein	Human breast cancer cells (MCF-7); human endometrial cancer cell (HeLa),	5, 10, 15, and 20 µM	chrysin had an antiproliferative and apoptotic effect on MCF-7 cells in a dose- and time-dependent manner; The root extract showed cell cycle arrest and apoptotic induction of HeLa cells.	[116,117]
Oxalis corniculata	Apigenin	Human Hepatocarcinoma (Huh7 and Hep3B) cells; Huh7 cells induced in mice model.	5, 10, and 20 µM (*in vitro*); 25 mg/kg/day (*in vivo*)	Apigenin dose-dependently inhibited Huh7 cell growth, invasion, and colony formation, and in xenografts model, it reduced tumor growth, promoted necrosis,	[118]
Paederia foetida	Lupeol and β-sitosterol	Human prostate cancer cells (PC-3 and DU-145 and monocytic THP-1 cell lines).	Lupeol (5–60 µM); β-sitosterol (10–120 µM)	Treatment of prostate cancer cells with MEPL, lupeol and β-sitosterol showed induction of apoptosis, decrease in cellular-viability and inhibition of cellular-migration.	[119]
Rubia cordifolia	1-hydroxytectoquinone	Malignant skin melanoma (A375).	10, 20, and 40 µM	1-hydroxytectoquinone exhibited promising cytotoxicity against A375 cells.	[120]
Spilanthes acmella	Eudesmanolide	HCT116, HEp2, and SGC-7901 human cancer cell lines.	3 µM and 6 µM	Eudesmanolides 1 and 2 (1β-hydroxyalantolactone and ivangustin respectively) showed strong cytotoxicity against HEp2, SGC-7901, and HCT116 cells, with compound 1 inducing apoptosis in HEp2 cells.	[121]
Solanum xanthocarpum	Ursolic acid	Metastatic Melanoma human cancer cells (SK-MEL-24).	–	The combination of UA and Sol synergistically inhibited CRC cell viability and induces apoptosis and autophagy. It also inhibits CRC cell metastasis	[122]
Taxus wallichiana	Tasumatrol B	NCI-H226, MDR 2780AD, HepG2, and eA498 cancer cell lines.	1.5–100 µM	Tasumatrol B demonstrated strong cytotoxic activity, highlighting its potential to enhance inhibition of the cancer drug target protein, EGFR tyrosine kinase.	[123]
Xanthium strumarium	Xanthatin	Human glioma cell line U251	1-20 µM	Anti-proliferation and pro-apoptosis effects of xanthatin in glioma by inhibiting autophagy via activation of PI3K-Akt–mTOR pathway,	[124]

cumin- upregulates apoptotic enzymes like caspases and downregulates cell cycle proteins like Cyclin D1 to inhibit cell cycle progression in addition to the upregulation of apoptotic genes such as Bax and downregulation of genes linked to inflammation, such as TNF-α, cytokines, and NF-κB, [129]. Nano micelles encapsulated with curcumin has shown to exhibit better cytotoxicity against cisplatin-resistant human oral cancer because of targeted localization [130]. Curcumin inhibited the growth of human A375 melanoma cells injected into mice subcutaneously by downregulating crucial intracellular signaling pathway linked to cell viability and death (PI3K/AKT/mTOR/P70S6K pathway) along with other mechanisms such as cell cycle arrest and autophagy [131].

Allicin and Asiatic Acid

Allicin from *Allium sativum* L. is shown to be effective against cholangiocarcinoma (CCA) where human liver bile duct carcinoma (HuCCT-1) was suppressed significantly in BALB/c nude mice model of CCA [132]. Asiatic acid is one of the effective bioactive compounds extracted from *Centella asiatica* (L.) Urb. Many studies have shown pharmacological effects of Asiatic acid with its anticancer effect being one of the prominent. Asiatic acid stimulates apoptosis in human SK- Melanoma MEL-2 and HepG2 human hepatoma cells by causing reactive oxygen species (ROS) to be produced [133] and releasing intracellular Ca^{2+} in addition to enhancing expression of p53 respectively [134].

Resveratrol from *Phyllanthus emblica*

Phyllanthus emblica L. collected from the wilds of Northeast region, India is one of the richest sources of resveratrol (RSV) [135]. RSV induces its anticancer effect by multiple mechanisms like cell cycle and apoptosis regulation, Inhibition of cell migration and metastasis etc. P53 mediated apoptosis in MDA-MB-231 cells is induced by activating a signaling cascade starting with RSV binding to the integrin αvβ3 receptor activates ERK1/2, nuclear COX-2 accumulation, and p53 phosphorylation, leading to the transcription of pro-apoptotic genes [136,137].

Bioactive Compounds from Amaranthus viridis

Amaranthus viridis L. contains many phytoconstituents that are responsible for its anticancer properties. Quercetin (QUE), kaempferol, and hydroxycinnamic acids (HCs)—coumaric acid, ferulic acid, sinapic acid, caffeic acid, chlorogenic acid, and rosmarinic acid—are among the chemical components of *A. viridis* that employs various mechanisms to inhibit cancer cells. QUE is said to inhibit lung A549 cells by inhibiting the production of tumor necrosis factor α (TNF-α) and IL-8 induced by lipopolysaccharide (LPS) in macrophages and lungs respectively [138,139,140]. QUE employs both extrinsic and intrinsic caspase dependent pathway to impede cell viability and induce apoptosis in MDA-MB-231cells. Here Ca^{2+} level was enhanced on the cytosolic side leading to increase in the potential of mitochondrial membrane. Caspase -3, – 8, and – 9 are said to be activated along with FAS, Bax, which is upregulated while Bcl-2 and XIAP is downregulated. Ultimately down-regulation of cyclin A and B and up-regulation of p57 led to cell cycle arrest [141]. Kaempferol (KMF) derived from *Amaranthus virdis* and *Ageratum conyzoides* is responsible for inducing cell cycle arrest and inhibiting the proliferation of various cancer cells. KMF arrests cell cycle in esophagus squamous cell carcinoma by inhibiting cell cycle transition points including G0/G, suppressing epidermal growth factor receptor (EGFR) activity along with the downstream signaling pathways [142]. KMF also showed anti-metastatic activity in MDA-MB-231 and MDA-MB-453 cells where RhoA and Rac1 activities are blocked along with downregulation of Rho signaling which is crucial for the reorganization of microfilaments and the migration of cancer cells [143].

Andrographolide from *Andrographis paniculata*

Andrographis paniculata (Burm.f.) Wall. ex Nees dispersed throughout Northeast India's many climate zones is the richest source of a bicyclic diterpenoid lactone known as Andrographolide. Andrographolide exerts its anticancer effect via limiting the activity of the hypoxia-inducible factor (HIF)-1α through its upstream PI3k/AKT/ mTOR pathway compromising tumor's adaptation to hypoxic condition [144].

Podophyllotoxin and its Derivatives

Podophyllotoxin isolated from a, highly uncommon plant *Podophyllum hexandrum* Royle of the family Berberidaceae rhizome possesses anticancer properties [145]. Several podophyllotoxin derivatives such as etoposide, teniposide, and etopophos have been synthesized to combat the issues of restricted bioavailability, drug resistance, and systemic toxicity. These semisynthetic drugs have been used in treating testicular cancer, neuroblastoma, hepatocellular carcinoma, Wilms tumors, and both Hodgkin's and non-Hodgkin's lymphomas, where it interferes with topoisomerase II activity by forming complexes with DNA [146].

Paclitaxel from *Taxus wallichiana*

Oil extracted from the bark of *Taxus wallichiana* Zucc. is used by the people of Arunachal Pradesh in the treatment of cancer. Paclitaxel extracted from leaves, seed and bark of *T.s wallichiana* is reported to cause aneuploidy in mitotic tumor cells by formation of multipolar spindle fiber that ultimately follow apoptosis pathway [147]. Treatment of ovarian cancer

with paclitaxel has also been established where it promotes the expression of tumor suppressor p21 and p27 genes leading to apoptosis [148].

Gallic Acid from *Bergenia ciliata*

Gallic acid extracted from *Bergenia ciliata* (Haw.) Sternb. which is endemic to Northern and Eastern temperate Himalayan region is reported to inhibit the proliferation of human glioblastoma U87 and U251 cells by downregulating Ras/MAPK and PI3K/Akt signaling pathway [149].

Synergistic effect of anticancer drugs with phytochemicals

Due to heterogenous nature of cancer, many chemotherapeutic drugs approved by FDA (Food and drug administration) have proven to show restricted efficacy [150]. Several side effects are associated with these drugs like drug resistance, poor targeting, and inconvenience faced by patient due to adverse effects. On the other hand, plant-based anticancer agents has proven to be a better alternative for cancer treatment for various reasons like lesser or no side effects, inexpensiveness, and better results.

Therapeutic efficacy of most anticancer drugs used in chemotherapy can be enhanced by stabilizing the drug in the system. This stabilization can be achieved and the difficulties posed by monotherapy using convention anticancer drug can be handled by co-administering the drug with anticancer phytochemical [151,152]. Combining cancer drug with phytochemical serve as a newer treatment for advanced cancer because it exerts beneficial effects through synergistic action of several chemical compounds that can render effective inhibition of cancer cells by reducing multidrug resistance and enhancing treatment efficacy.

Conclusion and future perspectives

With cancer being one of the leading causes of death and conventional chemotherapy having numerous complications, there is a critical need to find an alternative treatment for cancer which is natural, reliable, and low-cost. Phytochemicals are naturally occurring compounds isolated from plants that shows optimum pharmacological properties with minimum side effects. As confirmed by numerous investigations, phytochemicals exert their specific anticancer activity by regulating numerous cellular signaling pathways. Ethnopharmacological information as an important role in medicinal plant-based drug discovery. This review has shown that there are many interesting medicinal plants from Northeast region of India that can be sources of potent anticancer drug. Many distinct tribes in this region holds indigenous traditional knowledge on the uses of various medicinal plant available in that

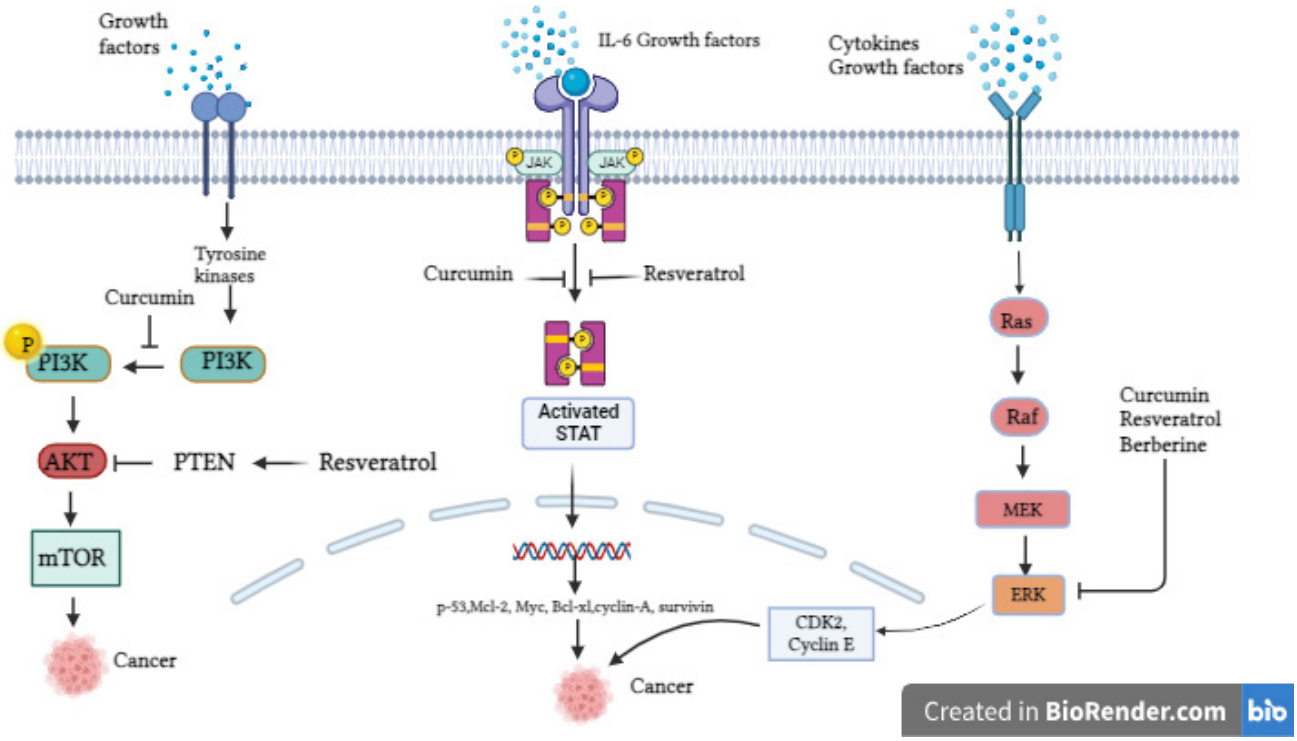

Figure 1. The underlying mechanism of chemoprevention exerted by phytochemicals: The image illustrates the three intracellular signaling molecules in various pathways responsible for carcinogenesis i) PI3K/Akt/mTOR ii) JAK/STAT pathway iii) ERK1/2 pathway being inhibited by some of the lead bioactive compounds derived from plants available in northeast India (created with https://BioRender.com).

Table 3. Synergistic effects of phytochemicals with conventional chemotherapy drugs in cancer treatment

Phytochemical	Chemotherapy Drug	Cancer Type/Cell Line	Effects	References
Berberine	Cisplatin	Ovarian cancer (OV-CAR3)	Induced G0/G1 cell cycle arrest	[153]
Berberine	Epirubicin	Bladder cancer (T24)	Improved inhibitory effect, induced G0/G1 cell cycle arrest	[154]
Curcumin	Docetaxel	Prostate cancer (DU145, PC3)	Inhibited cell proliferation, induced apoptosis by modulating RTKs, PI3K, NF-κB, COX-2, phosphor-AKT and p53	[155]
Curcumin	5-Fluorouracil (5-FU)	Colorectal cancer	Enhanced chemosensitivity, disintegrated colon sphere, inhibited growth, enhanced apoptosis	[156]
Curcumin + DTX	MEGA-PLA copolymer	Ovarian cancer (A2780)	Inhibited tumor proliferation and angiogenesis, induced apoptosis in vitro and in vivo	[157]
Resveratrol	Temozolomide (TMZ)	Malignant gliomas	Suppressed autophagy, increased apoptosis via inhibition of ROS and ERK pathway	[158]
Quercetin, Sulforaphane	Cisplatin, 5-FU	Cervical cancer (HeLa)	Enhanced cytotoxicity, initiated apoptosis, reduced metastasis	[159]
Allicin	Methylsulfonylmethane (MSM)	Breast cancer (MCF7 CD44+ cells)	Induced cell cycle arrest at G2/M and S phases, enhanced Caspase-3 mRNA expression	[160]
Epigallocatechin gallate (EGCG)	5-Fluorouracil (5-FU)	Colon cancer (HCT-116, DLD1)	Decreased IC50 values, reinforced sensitivity to 5-FU	[161]
Various phytochemicals (andrographolide, EGCG, chlorophyllin, colchicine, curcumin, paclitaxel)	Oxaliplatin	Ovarian cancer (A2780, A2780USR)	Increased synergism, with colchicine and paclitaxel combinations showing highest activity	[162]

region. Bioactive compounds from these medicinal plants can be potential leads in development of safer anticancer drug as reported in various studies. Phytochemicals from selected medicinal plant have been screened for their anticancer activity which have reached clinical trial level and have been documented for their effectiveness [163]. Combining cytotoxic antitumor agents and inhibitors from phytochemicals can together participating in inhibitory mechanisms that can modulate different signaling pathways. Incorporating nanotechnology in drug delivery system, diagnosis, as well as cancer imaging can provide maximum therapeutic efficacy by alleviating cancer targeting. With knowledge of mechanism for cancer development and coadministration of anticancer drug along with phytochemical offer a novel way of treating cancer. Moreover, identifying molecular targets of the newly-discovered anticancer phytochemicals and their associated biomarkers can provide a new aspect to the standard cancer therapy. In the near future, each patient should be provided with individualized chemotherapy which can improve the therapeutic quality because well-matched drugs can be prescribed to each patient that can help in eliminating the ineffective ones [164]. This unique therapy can improve the hazardous condition of cancer patient.

Conflict of Interests

The authors declare that there are no competing interests associated with this work.

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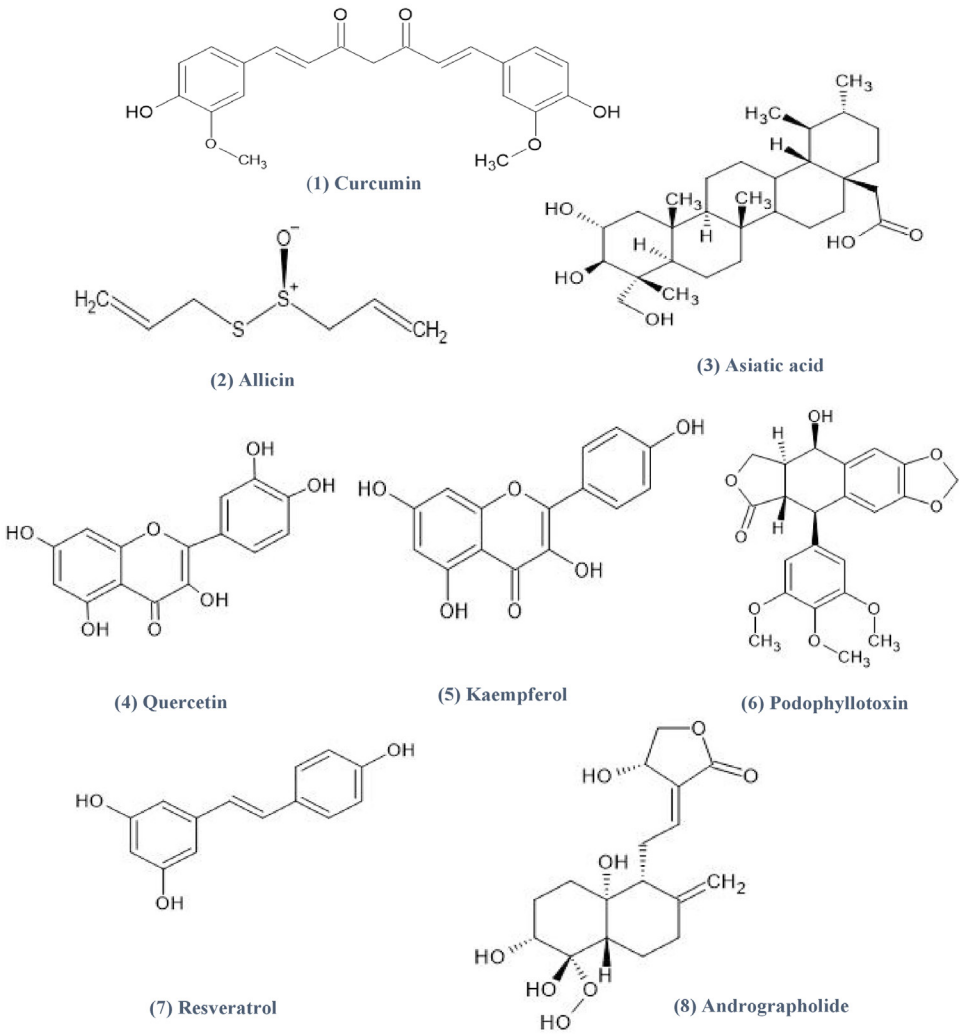

Figure 2. Chemical structures of some lead anticancer phytochemicals.

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