Chapter 4
Potentiality of Anticancer Plant-Derived Compounds of North-East India

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4.1 Introduction

Cancer is a severe metabolic syndrome and the leading cause of mortality and morbidity worldwide with the number of cases increasing every year (Sharma et al. 2014; ACS 2016). In developed nations, this disease ranks second in death cases after cardiovascular disorders (Mbaveng et al. 2011; Siegel et al. 2016). The incidence of mortality and prevalence from major types of cancer as estimated by International Agency for Research on Cancer of 184 countries of the world revealed that there were 8.2 million cancer deaths, and 14.1 million new cancer cases, worldwide and it is projected that by 2030 there will be 26 million new cancer cases and 17 million cancer deaths per year (Thun and De Lancey 2010). Cancer is characterized by uncontrolled proliferation and dedifferentiation of normal cell. A typical cancer cell has marked attributes, viz. sends signals of proliferation and differentiation and is capable to sustain proliferation; they have the power of invasion and angiogenesis, and they overcome apoptosis (Sharma et al. 2014). Transformation from normal cell to malignant cell involves a sequence of alterations producing genetic instabilities which accumulate in a cell. Alterations such as mutation in DNA repair genes, oncogenes, apoptotic genes, tumour suppressor genes and gene involved in cell growth and differentiation are prominent (Sharma et al. 2014).

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Cancer is caused by both internal (e.g. hormones, gene mutations and immune conditions) and external (e.g. smoking, radiation and pollution) factors.

North-East India is one of the nine global biodiversity hotspots lying between 22–30°N latitude and 89–97°E longitude. This region is blessed with varying flora with diversified topography and climatic conditions marked by high humidity, moderate temperature and high rainfall. There are abundant dense forests, swamps, marshes, etc. that engulf the region with vegetation ranging from tropical to the alpine forests. Different tribes of North-East India rely mostly on the ethnic traditional herbal medicine due to lack of adequate modern medical facilities (Syiem and Kharbuli 1999; Rosangkima et al. 2010; Tushara et al. 2010). The crude herbal preparations are applied by the herbal practitioners with additives, viz. milk, curd, ghee honey, etc., as adjuvant in order to enhance the effect of the respective herbal preparations (Behere et al. 2013). The aim of the present chapter is to focus on the potentiality of major plant-derived compounds from diversified medicinal plants of North-East India for their anticancer and chemopreventive activity and their mode of action. Moreover, their large-scale production, uses of structural analogs, and molecular docking studies of some of the selected plant-derived compounds are also discussed.

4.2 Plants as an Imperative Source of Chemopreventive Phytochemicals

Since ancient times herbal formulations are used for medicinal purposes. Herbal practitioners apply various herbal formulations which are based on different philosophies and cultural origins to heal diseases. Traditional knowledge, viz. Ayurveda, Kampo, Egyptian medicine and traditional Chinese medicine, is the science of good health and well-being (Hashimoto et al. 2000; Rosangkima et al. 2010; Sharma et al. 2014). In the recent times, hunt for novel phytochemicals for drug development based on the concepts of traditional knowledge has gained wide acceptance. Natural products derived from plants are non-toxic thereby making them ideal candidates for modern drug discovery. Only 10% of the 250,000 plant species have been investigated for therapeutic applications, and more than 50% of all the modern drugs are derived from plants. Varieties of phytochemicals and their derived metabolites are present in the bark, root, leaves, stem and flower which serve an array of pharmacological activity in human health system. Phenolics, alkaloids, flavonoids, glycosides, tannins, oils and gums are responsible compounds for various therapeutic purposes. A significant antitumour activity has been shown by altered forms of these compounds. Curcumol, betulinic acid, kaempferol, ellagic acid, dillenetin, L-borneol, taxol, tangeretin, naringin and resveratrol are some of the remarkable chemopreventive phytochemicals as lead molecules for the development of anticancer drugs (Table 4.1).

Table 4.1 Chemopreventive phytochemicals derived from plants available in North-East India

Phytochemicals	Plants	Suppressed cancerous cell lines/cancer models	Uses	References
Kaempferol	*Ageratum conyzoides*	Lung cancer (A-549), gastric carcinoma (SGC-7901), colon carcinoma (HT-29), human glioma carcinoma (U-251), breast cancer (MDA-MB-231), prostate cancer (DU-145), hepatic carcinoma (BEL-7402), mouse leukaemia (P-388)	In clinical use	Adebayo et al. (2010)
Nimbolide	*Azadirachta indica*	Lung cancer (U937), leukaemia (HL-60, THP1), skin melanoma (B16), prostate cancer (PC-3)	In preclinical development	Baral and Chattopadhyay (2004), Giri and Lakshmi Narasu (2000) and Kumar et al. (2006)
Taxol	*Taxus baccata*	Breast cancer (HER2, MDA-MB- 435), ovary (SK-OV-3 w)	In clinical use	Baselga et al. (1998) and Aggarwal and Shishodia (2005)
Δ^9-Tetrahydrocannabinol	*Cannabis sativa*	Breast cancer (MCF-7, EFM-19, MDA-MB-231), skin cancer (PDV.C57, HaCa4), brain/spine tumour (U87, U373)	In preclinical development	Casanova et al. (2003), Massi et al. (2004), Cheung and Tai (2007) and Yesil-Celiktas et al. (2010)
Curcumin	*Curcuma longa*	Breast cancer (BT-20,T-47D, SK-BR3 and MCF-7), leukaemia (HL60)	In preclinical use	Cui et al. (2006) and Magesh et al. (2009)
6-Shogaol, (6)-gingerol	*Zingiber officinale*	Breast cancer (MCF-7 and MDA-MB-231), colon cancer (HCT 116, HT 29), ovarian cancer (SK-OV-3), lung cancer (A549), melanoma (SK-MEL-2), colorectal adenocarcinoma (HCT15)	In clinical use	De Petrocellis et al. (1998), Kim (2008) and Ligresti et al. (2006)

(continued)

Table 4.1 (continued)

Phytochemicals	Plants	Suppressed cancerous cell lines/cancer models	Uses	References
Dillenetin and betulinic acid	*Dillenia indica*	Lung cancer (U937), promyelocytic leukaemia (HL60, K562)	In preclinical development	Gandhi and Mehta (2013)
Alexin B, emodin	*Aloe vera*	Liver cancer (HepG2), breast cancer (MCF-7), cervical cancer	In preclinical development	Hussain et al. (2015) and Noorolahi et al. (2016)
Taxol	*T. baccata*	Breast cancer (BT-474, SK-BR-3 and MCF7)		Klauber et al. (1997)
Dillenetin and betulinic acid	*Dillenia pentagyna*	T-cell lymphoma	In preclinical development	Mehta et al. (1997) and Rosangkima and Prasad (2007)
Catechin	*Potentilla fulgens*	Breast cancer (MCF-7), human glioblastoma cancer (U-87)	In clinical use	Mittal and Tripathy (2015)
Dihydroflavonol	*Blumea balsamifera*	Breast cancer (MCF-7), epidermal carcinoma of the mouth (KB), myeloid leukaemia (K562), lung cancer (NCI-H187), hepatocellular carcinoma (McA-RH7777)	In preclinical development	Norikura et al. (2008)
Eugenol, orientin, vicenin	*Ocimum sanctum*	Lung cancer (A549), human fibrosarcoma cells (HFS)	In preclinical development	Roy et al. (2007)
Oleic acid and beta-sitosterol	*Mirabilis jalapa*	Human laryngeal carcinoma (Hep-2), breast cancer (MCF-7)	In preclinical development	Rumzhum et al. (2008) and Gogoi and Nakhuru (2016)
Vinblastine, vincristine	*Catharanthus roseus*	Lung cancer (NCI-H69/P)	In clinical use	Trevor and Theodore (1993)
Epicatechin, procyanidin B_2, B_4	*Litchi chinensis*	Breast cancer (MCF-7), leukaemia (U937, K562 and HL-60), colorectal cancer (Colo320DM and SW480)	In preclinical development	Twentyman et al. (1987), Lipinsky et al. (1997) and Hsu et al. (2012)

(continued)

Table 4.1 (continued)

Phytochemicals	Plants	Suppressed cancerous cell lines/cancer models	Uses	References
Etoposide, podophyllin, teniposide, podophyllotoxin	*Podophyllum hexandrum*	Lung cancer, testicular cancer, neuroblastoma, hepatoma	In clinical use	Uden (1989) and Abdullah and Abidin (2010)
Xanthatin, xanthinosin, 4-oxobedfordia	*Xanthium strumarium*	Cervical cancer	In preclinical development	Vaishnav et al. (2015)
Carnosic acid, rosmarinic acid	*Rosmarinus officinalis*	Breast cancer (MCF7 and MDA-MB-468), leukaemia (HL60, K-562), prostate cancer (DU-145), lung cancer (NCI-H82), liver cancer (Hep-3B), ovarian cancer (r A2780)	In preclinical development	Zhao et al. (2007), Roya et al. (2008) and Tai and Cheunga (2012)

4.3 Mechanism of Action and Molecular Targets of Chemopreventive Phytochemicals from North-East India

The precise mechanism of action of the bioactive molecules performing anticancer functions is an interesting area of current research. The usual targets of these molecules are the cytosolic and nuclear factors of a cancer cell. They either directly absorb the reactive oxygen species or stimulate the antioxidant enzymes, viz. catalase, glutathione and superoxide dismutase, in a transformed cell. The metabolic conversion of a procarcinogen is blocked by a phyto-molecule, or it suppresses malignant transformation of a preneoplastic cell. The cellular and signalling events involved in growth, invasion and metastasis are also regulated by these molecules. Curcumin (diferuloylmethane), a polyphenol present as a major phytochemical in the rhizome of *Curcuma longa*, is the most prominent chemopreventive bioactive molecule studied (Aggarwal et al. 2003; Fridlender et al. 2015). It has been used as a medicine for treatment of various diseases (Sharma et al. 2005; Fridlender et al. 2015; Lee and Kim 2016). Kaempferol, the major phytochemical in *Potentilla fulgens*, acts on proto-oncogene tyrosine protein kinase (Src), Erk1/2 and Akt pathways in pancreatic cancer cells and retards their growth and migration (Hossan et al. 2014). Ellagic acid from *P. fulgens* induces apoptosis in breast and prostate cancer cells and inhibits metastasis processes of various cancer types. Rosmarinic acid present in *Ocimum basilicum* reduces the activity of DNA methyltransferase and interferes OPG/RANKL/RANK networks (Osakabe et al. 2004; Baliga et al. 2013). Besides, it also acts in colon cancer cells by reducing COX-2 activity and Erk phosphorylation. Moreover, it targets PKA/CREB/MITF pathway and NF-kB activation in melanoma

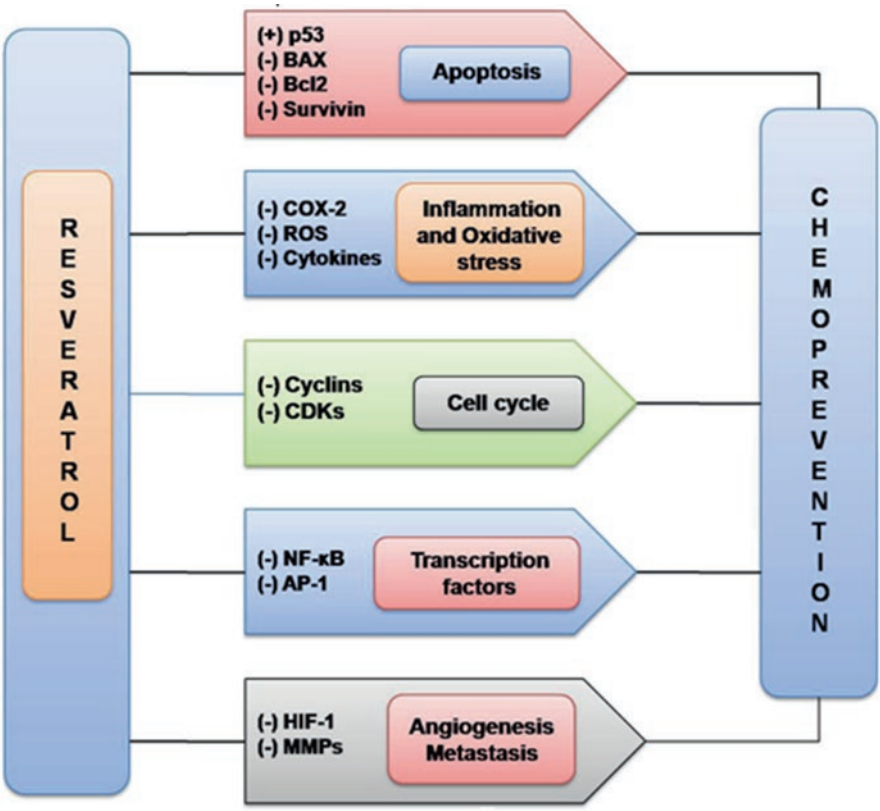

Fig. 4.1 Molecular targets of resveratrol leading to chemoprevention

and leukaemia U938 cells, respectively, thereby stimulating anti-inflammatory and antioxidant activities which consequently inhibit skin cancer (Osakabe et al. 2004; Roland et al. 2010; Baliga et al. 2013; Radhakrishnan et al. 2014). Gingerol present in *Zingiber officinale* induces caspase-dependent apoptosis in colon cancer cells by targeting the Erk1/2/JNK/AP-1 signalling (Fridlender et al. 2015). Tetrahydrocannabinol isolated from *Cannabis sativa* has been used in the past two centuries as supporting drugs for patients that receive either radiation or chemotherapies. Side effects related to these treatments such as vomiting, cachexia, nausea and loss of appetite are eased by cannabinoids (Robson 2001; Tramer et al. 2001; Ligresti et al. 2003; Massa et al. 2005; Grotenhermen and Muller-Vahl 2012). Studies imply that in the gastrointestinal system cannabinoid receptors are involved in inhibition of cell proliferation of colorectal carcinoma (Massa and Monory 2006; Varoni et al. 2016). Multiple mechanisms are performed by resveratrol in order to arrest carcinogenesis (Fig. 4.1). Paclitaxel ($C_{47}H_{51}NO_{14}$) is known as taxol, probably the most well-known anticancer drug derived from the bark of *Taxus brevifolia* Nutt. It inhibits the microtubule disassembly by binding the polymerized microtubules

(Xiao et al. 2012; Prota et al. 2013). Taxol binds to the microtubule-associated protein (MAP) microtubule complex causing further stabilization of microtubules thereby preventing mitotic spindle formation and thus inhibits mitosis as well as cell proliferation (Priyadarshini and Aparajitha 2012; Weaver 2014). Induction of multipolar divisions leads to formation of abnormal spindles bearing additional poles, and the consequence is unnatural chromosomal segregation which leads to the formation of abnormal aneuploid daughter cells that follow the apoptosis pathway (Priyadarshini and Aparajitha 2012).

4.4 Purification of Anticancer Phytochemicals

The curative efficacy of medicinal plants is determined by the quality and quantity of bioactive molecule(s) which varies with altitude, latitude, climactic conditions and seasons. Varieties of chemopreventive bioactive molecules are distributed across different parts of a plant accounting for varying levels of pharmacological activity. Development of the phytochemicals as antitumor entities becomes a daunting task owing to the synergistic effects of such bioactive phyto-constituents rather than the purified one. Purification of bioactive phytochemicals includes isolation and assay, combinatorial chemistry and bioassay-guided fractionation. Prior to fractionation of the crude plant extract, the bioactivity of the extract is confirmed by subjecting it to bioassays. Various analytical platforms are used for examination of the eluted fractions, viz. FT-IR, mass spectroscopy, HPLC and thin-layer chromatography (Fig. 4.2). Solvents should be used in an increasing polarity order of silica, Sephadex, Superdex or any other suitable matrix that can be used for fractionation. Purification is followed by in vivo examination of extracts for evaluation of anticancer activity. The killing activity of tumour and other parameters like pharmacokinetics, safety and adverse effects, dose concentration, drug interactions, etc. must be explored before the development of novel anticancer drugs. However, the major bottleneck for rapid manufacturing of medicines using natural products is the poor solubility and bioavailability of plant secondary metabolites (Guo et al. 2006). In order to meet market demands, the development and use of synthetic or semi-synthetic analogs to plant-derived substances are adopted. Morphine is a well-known example that has been modified to morphine-6-glucuronide in order to enhance its therapeutic efficacy (Parc et al. 2002). Taxol, an important plant-derived (*Taxus* sp.) anticancer drug, is present in low amounts in all *Taxus* species along with its insolubility in water. These limitations in taxol manufacturing are overcome by combining the use of 10-deacetylbaccatin III and a semi-synthetic process for production of the drug. Docetaxel is the semi-synthetic soluble analog of taxol which is widely used, and additional strategies for improvement are needed to enhance its features and also to meet future market demands of this important drug (Aggarwal et al. 2003; Sharma et al. 2005; Malik et al. 2011; Fridlender et al. 2015). Curcumin analogs have been prepared owing to its insolubility in water. Besides due to reduced absorption in the liver and in intestinal walls and systemic

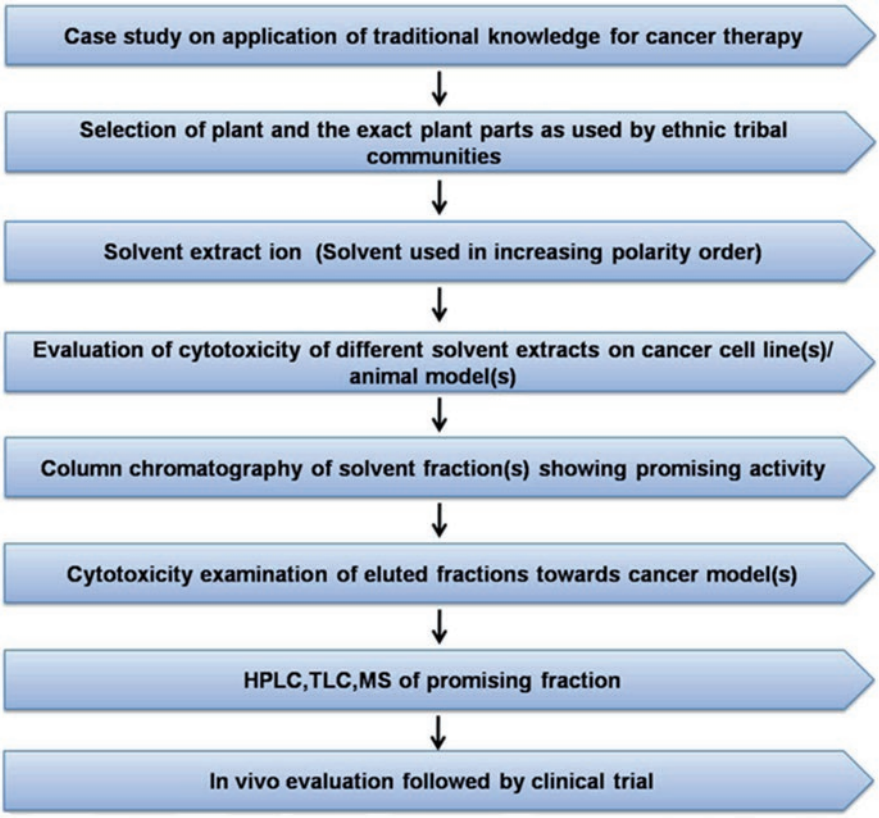

Fig. 4.2 Development of novel anticancer drugs derived from bioactive phytochemical

elimination, curcumin has poor bioavailability (Gordaliza 2007). However, the modified analog (beta-diketone monocarbonyl dienone) of curcumin has a good bioavailability and therapeutic effect as demonstrated in rodents (Twentyman et al. 1987; Mosley et al. 2007).

4.5 In Vitro Propagation of Anticancer Plants

The anticancer plants are seems to be endangered. Therefore, there is a need to raise these plants for drugs and other therapeutic applications through various standardized protocols under in vitro conditions (Kingston 2000; Malik et al. 2011). The induction of callus and proliferation of gametophytes of *T. baccata*, found abundantly in north-eastern states of Nagaland and Arunachal Pradesh, was reported by past investigators (Rohr 1973; David and Plasitra 1974). However, David and Plastira (1976) studied the mineral and phytohormone composition of culture

Table 4.2 Standardized in vitro shoot proliferation conditions of *P. fulgens*

Explants	Medium	Sucrose (%)	Auxin	Cytokinin	Root proliferation	Reference
Leaf	MS	3	IAA (1 mg/l)	BAP (1 mg/l)	Axillary	Wilken et al. (2011)
Leaf	MS	3	NAA (1 mg/l)	Kinetin (1 mg/l)	Adventitious	Klauber et al. (1997)

medium to improve callus proliferation using mature stems as explants. Moreover, callus induction studies have been also performed using different explants, viz. hypocotyls, cotyledons, young or mature stems, and the roots from young seedlings, by past investigators (Brunakova et al. 2004, 2005). These studies concluded that the young tissues are more responsive and prone to callus induction than mature plants or adult trees (Brunakova et al. 2004). However, in vitro conditions for auxiliary and adventitious shoots of *P. fulgens*, an endangered anticancer herb of higher Himalayas, using leaf as explants (Wilken et al. 2011) were tabulated in Table 4.2.

4.6 Conclusions and Future Prospects

The plant of North-East India or their derived compounds have the potential to be used as anticancer agents. The use of single drug to treat a single disease is questionable, and is a matter of debate since several decades. The recent trends in genomics, which is concerned with the genetic diversity or polymorphisms, clearly indicated that different human population need different drugs to cure the diseases. In this regard, the use of herbal medicines is gaining popularity because of its cost-effectiveness and potentials in the conventional medicinal practices. However, lacks of consistency in terms of their composition, efficacy, quality, safety, consistent manufacturing practices, regulations and approval processes lead the idea to combine the traditional and modern medicine practices. Therefore, the exploration of the plants found in North-East India is highly desired for the search of novel bioactive anticancer compounds and their mechanisms of action involved in the treatment of various types of malignant cells.

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