Journal of Medicinal and Aromatic Plant Sciences 42(1-2), 2020, 1-29

REVIEW ARTICLE

Medicinal plant-derived therapeutics for treatment of neoplasms in modern and traditional systems of medicine

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Article History

Received: February 12th, 2020
Revised: June 10th, 2020
Accepted: June 18th, 2020

Key Words

Ayurveda
Cyclopamine
Flavopiridol
Podophyllotoxins
Taxanes
Verazine

ABSTRACT

Cancer poses an important challenge for mankind. Plants have provided major remedies and clues for its treatment. Plant-derived compounds (phytomolecules) are an important source of several clinically-useful anticancer drugs. Here we summarize the current status of plant-based therapies for cancer treatment. Examples of clinically-useful anticancer phytomolecules are taxol, vincristine, vinblastine, camptothecin derivatives – topotecan and irinotecan, and etoposide derived from epipodophyllotoxin. Several promising compounds like, combretastatin A-4 phosphate and flavopiridol are in various stages of clinical development. IPI-926, a semi-synthetic analog of steroid alkaloid cyclopamine, has shown promise against several cancers including pancreatic cancer and leukemia and has been under clinical trials. Besides, there are several other promising molecules that are receiving attention. Most of the drugs are directly used after isolation and purification from renewable resources or they can be produced after efficient chemical modification of the same. Simultaneously, it must be appreciated that traditional systems of medicine like Ayurveda have also described cancer-like diseases (with alternative names like Arbuda*,* Granthi *and* Gulma*) and prescribed plant-based therapies for curing them. Logically, if modern science takes cues from Ayurveda and targets such plants, a higher probability of hit rates in anticancer drug discovery is expected.*

INTRODUCTION

Cancer is the second major cause of deaths after cardiovascular diseases (Amin et al., 2009). The disease is characterized by unregulated proliferation of cells. Plants have provided a potent arsenal of phytomolecules against cancer (Hartwell, 1982; Pezzuto, 1997). Over 60% of currently used anticancer drugs are obtained from natural sources, including plants, microbes and marine life, among which plants stand out as the most important source of effective anticancer agents (Cragg et al., 2005; Newman et al., 2003).

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The search for plant-derived anticancer drugs began in 1950 with the discovery and development of bisindole alkaloids [vincristine (VCR) and vinblastine (VLB)] from *Catharanthus roseus* (Apocynaceae) and the isolation of cytotoxic podophyllotoxins. The National Cancer Institute (NCI, USA) initiated its extensive plant collection program from the temperate regions in 1960 that led to the discovery of many novel chemical entities having varied cytotoxic activities (Cassady and Douros, 1980), including taxanes and camptothecins. Later on, the plant collection program was also focused on tropical and sub-tropical regions of the world. Earlier some excellent reviews have been published in this area (Cragg and Newman, 2005; Srivastava et al., 2005; Amin et al., 2009). Alkaloids are by far the largest class of phytomolecules possessing anticancer activity and contributing to drug development. There are various ways to classify plant-derived anticancer agents. For example, they could be classified as per their mode of action as mitotic disrupters, methyltransferase inhibitors, histone deacetylase inhibitors (HDACi) and DNA damaging/pro-oxidant drugs (Amin et al., 2009). However, the present review focuses on the following categories of plant-derived anticancer agents/molecules: those in clinical use (**Fig. 1**); those in clinical development (**Fig. 2**); those in pre-clinical development (**Fig. 3**); those under active research in recent times (**Fig. 4**).

Clinically-used anticancer agents from plant sources

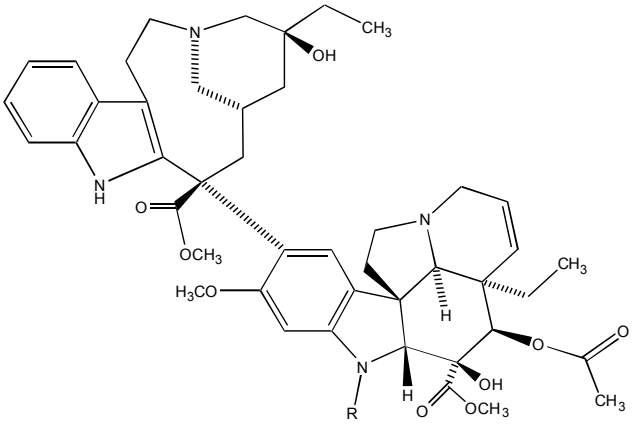
The bisindole alkaloids – VCR and VLB isolated from *C. roseus* (Sadabahar), were the first agents to be used clinically. Primarily, *C. roseus* was used by various cultures as an anti-diabetic plant (Gueritte and Fahy, 2005). During one such investigation as a source of oral hypoglycaemic phytomolecules, it was found that its extracts lowered the leukocyte count and led to bone marrow depression in experimental rats. Subsequently, they were found to have potent activity against lymphocytic leukemia in small animals like mice and finally it paved the way for isolation of VCR and VLB as active anticancer agents. Vinorelbine (VRLB) and vindesine (VDS) are semi-synthetic analogs of the bisindoles. They are popular in combination therapy with other anti-cancer drugs for treating various types of cancers.

Podophyllum species (*P. peltatum* and *P. emodii*) (Berberidaceae) have been used for treating skin cancers and warts since a long time. Podophyllotoxin is their major active phyto-constituent whereas etoposide and teniposide are semi-synthetic derivatives of epipodophyllotoxin (an isomer of podophyllotoxin) (Lee and Xiao, 2005). These semisynthetic derivatives are the drug of choice for treating bronchial and testicular cancers as well as lymphomas.

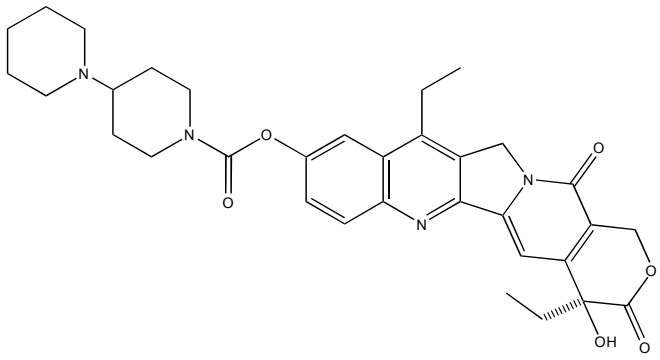
Paclitaxel (taxol) was first isolated from the bark of *Taxus brevifolia* (Pacific Yew; Taxaceae). Taxanes are the most important plant-based chemotherapeutic agents (Kingston, 2005). There are reports of use of various parts of *T. brevifolia*, *T. canadensis* and *T. baccata* by native American tribals for the treatment of benign tumors. On the other hand, the leaves of *T. baccata* have found use in Ayurveda for treating cancer-like symptoms. Paclitaxel, and its precursors, like baccatins, are found in the leaves of different *Taxus* species. Semi-synthesis of taxol and its analogs like docetaxel from the baccatins offers a renewable natural source of these important drugs. Taxol is effective against Kaposi's sarcoma, breast, ovarian, and non-small cell lung cancer (NSCLC).

Camptothecin-derived drugs constitute another important class of anticancer drugs. Camptothecin is sourced from the Chinese plant, *Camptotheca acuminata* (Nyssaceae) (Rahier et al., 2005). Although camptothecin itself causes severe bladder toxicity, it's more effective derivatives, topotecan (used for the treatment of ovarian and small cell lung cancers) and irinotecan (used for the treatment of colorectal cancers), are highly popular in cancer chemotherapy.

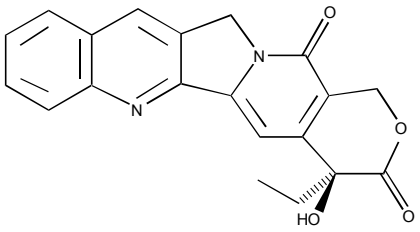
Apart from the aforementioned ones, the other prominent phyto-derived anticancer agents in clinical use are homoharringtonine, obtained from *Cephalotaxus harringtonia* var. *drupacea* (Taxaceae) (Sausville et al., 1999) and elliptinium, a derivative of ellipticine, obtained from *Bleekeria vitensis*. A racemic mixture of harringtonine and



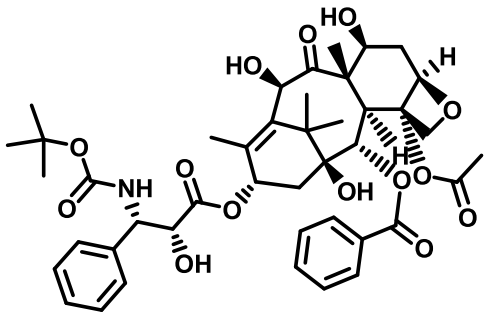
R = CH_3 Vinblastine
R = CHO Vincristine



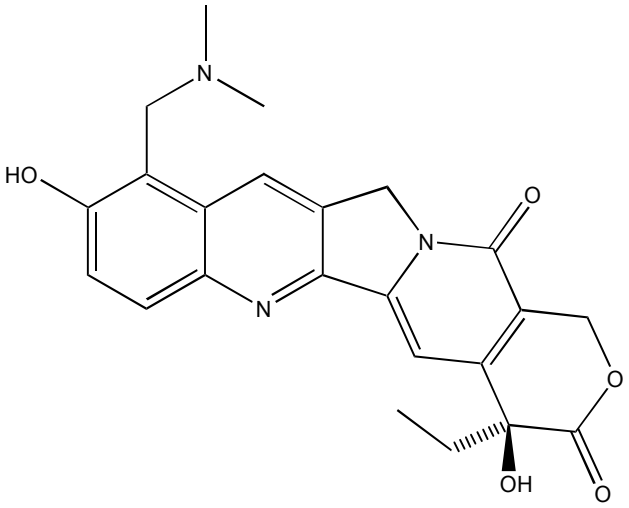
Irinotecan



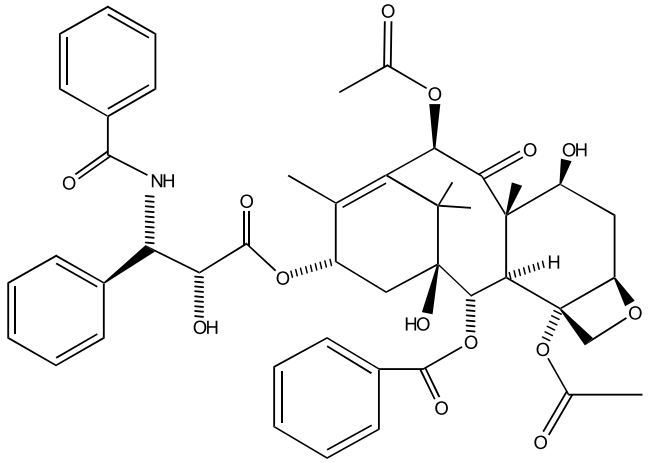
Camptothecin



Docetaxel

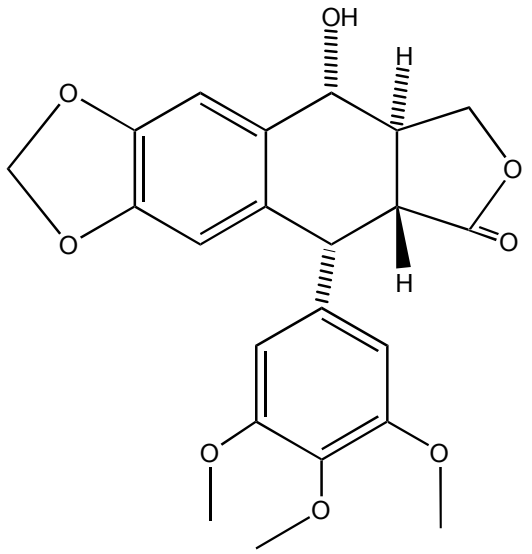


Topotecan

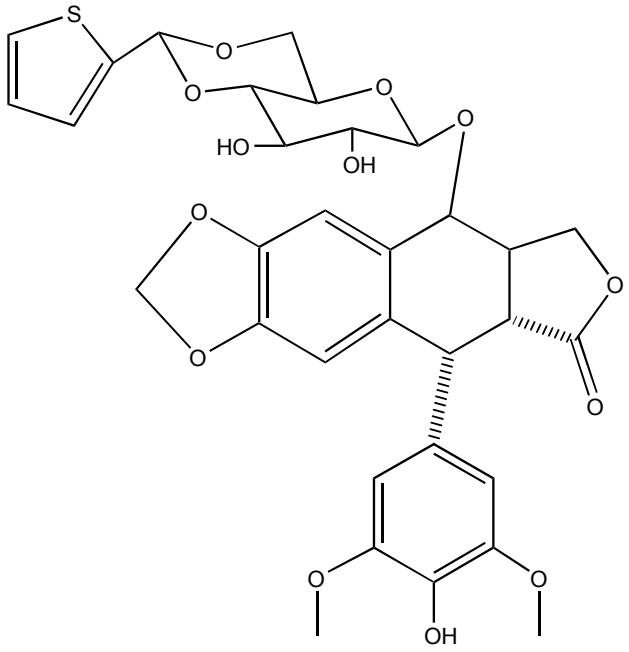


Taxol

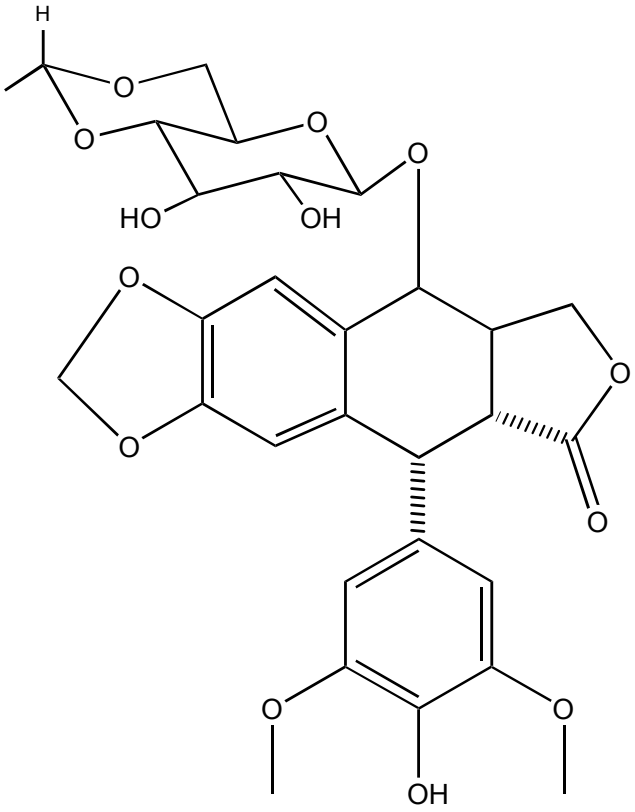
Figure 1: Plant-derived anticancer agents that are presently in clinical use



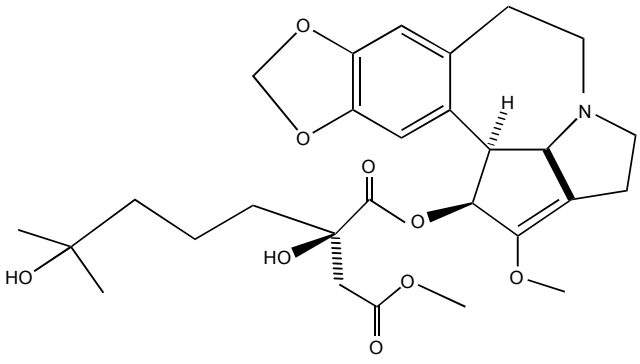
Podophyllotoxin



Tenoposide



Etoposide



Homoharringtonine

Figure 1 (Contd.): Plant-derived anticancer agents that are presently in clinical use

homoharringtonine (HHT) is effective against myelogenous leukemia whereas elliptinium is a breast cancer treatment drug in the French market.

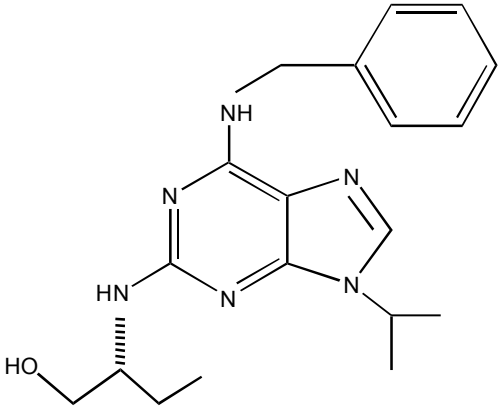
Plant-based anticancer agents in clinical development

The novel flavonoid structure of flavopiridol, a synthetic molecule, is based on the natural product, rohitukine, obtained from *Dysoxylum binectariferum* (Meliaceae) that is a close relative of the Ayurvedic plant *D. malabaricum*, prescribed for treatment of rheumatoid arthritis. Flavopiridol possesses tyrosine kinase activity and is a potent growth inhibitor of lung and breast carcinoma cell lines (Sausville et al., 1999). *Combretum caffrum* (Combretaceae) is the source of combretastatins (Pinney et al., 2005). Many *Terminalia* species (Combretaceae) have also been reported to be effective in the treatment of diseases with cancer-like symptoms. The combretastatins are known to possess anti-angiogenic activity, which leads to tumor necrosis. One of the water soluble analogs, combretastatin A4 phosphate seems to be quite promising. This chemical species has attracted the attention of numerous medicinal as well as combinatorial chemists (Li and Sham, 2002).

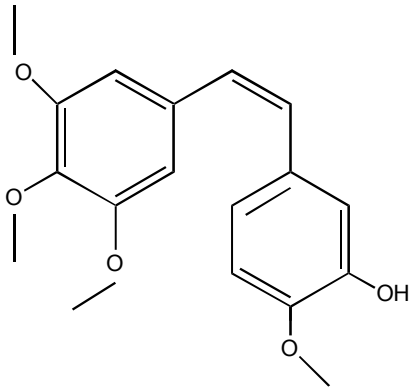
The synthetic molecule, roscovitine, is based on the radish-derived natural product, olomucine (Meijer and Raymond, 2003). These molecules have inhibitory activity against cyclin-dependant kinases that are involved in the progression of the cell cycle. Purvalanols are even more effective molecules of this series derived through combinatorial chemistry methods (Chang et al., 1999).

Plant-based anticancer agents in preclinical development

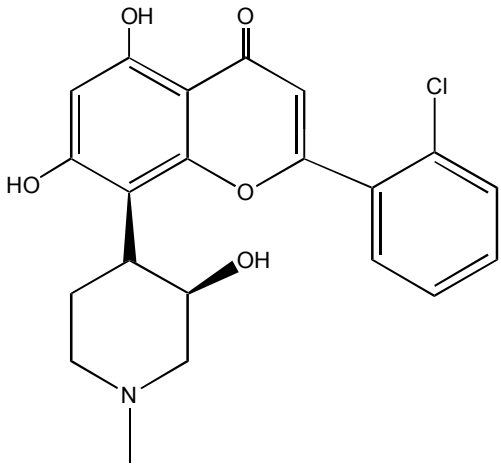
During the development of several plant-derived agents it has been emphasised that they should be highly effective and free from toxicity. Due to lack of these criteria, many agents have been dropped from preclinical trials. Maytansine, obtained from *Maytenus serrata* (Celastraceae) (Cassady et al., 2004), was found to be highly effective against cancer cell lines, but it was dropped due to poor efficacy in clinical studies. Some conjugates of maytansine have been found



Roscovitine



Combretastatin A4



Flavopiridol

Figure 2: Plant-derived anticancer molecules in clinical development

to be useful against gastric, prostate, pancreatic, biliary and colorectal cancers.

Thapsigargin (TG) isolated from *Thapsia garganica* (Apiaceae) represents another

interesting case (Denmeade et al., 2003). It has the capability to induce apoptosis in proliferating prostate cancer cells but is devoid of selectivity. However, its small peptide conjugate gives a water-soluble prodrug that imparts specificity to it.

A beneficial relook at the phytomolecules dropped earlier has been facilitated through new scientific developments. One such example is provided by bruceantin, which is obtained from *Brucea antidysentrica* (Simaroubaceae) (Cuendet and Pezzuto, 2004).

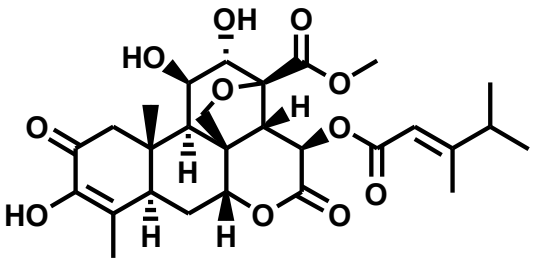
Betulinic acid has been isolated from several taxonomically diverse plant species (Cichewicz and Kouzi, 2004). Its major source is the birch tree, *Betula* spp. (Betulaceae). Betulinic acid has been reported to possess a wide variety of activities including, anticancer potential.

Indirubins, obtained from *Indigofera tinctoria* (Fabaceae), are used to treat chronic myelogenous leukemia. Some substituted indirubins show comparable activity to flavopiridol and roscovitine (Newman et al., 2002).

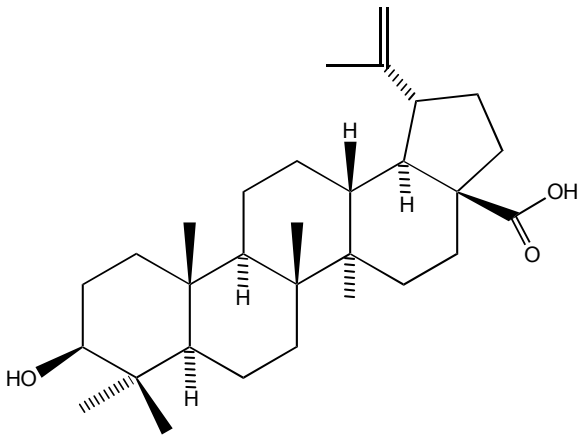
A synthetic derivative of oleanolic acid, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) as well as its methyl ester exhibit potent *in vivo* and *in vitro* antitumor activity (Couch et al., 2005). CDDO exhibited significant activity against cisplatin-resistant epithelial ovarian cancer (EOC) cell lines (Melichar et al., 2004).

Tabebuia species (Bignoniaceae) like *T. impetiginosa*, *T. rosea* and *T. serratifolia* have been reported to possess the naphthoquinones, lapachol and β-lapachone, whereby lapachol was shown to possess *in vivo* anticancer activity in small animal models but during clinical trials it showed high levels of toxicity and was dropped (Suffness and Douros, 1980). Renewed interest was evident for β-lapachone due to its significant activity against a range of tumor cell lines as well as several multi-drug resistant (MDR) lines (Ravelo et al., 2004).

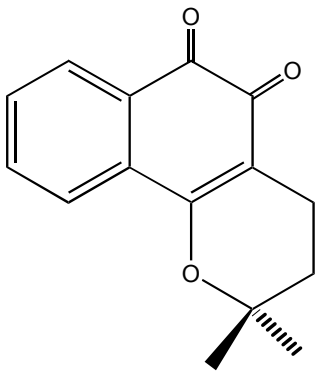
Many cancer patients develop resistance during treatment with standard drugs. Such a situation warrants the use of a MDR inhibitor. The pervilleines obtained from *Erythroxylum pervillei*



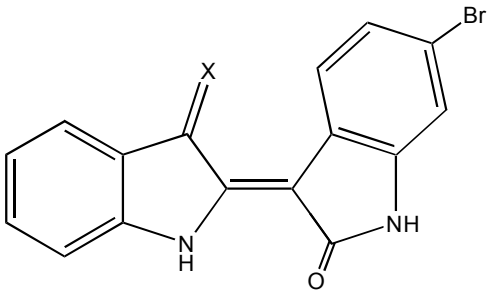
Bruceantin



Betulinic Acid

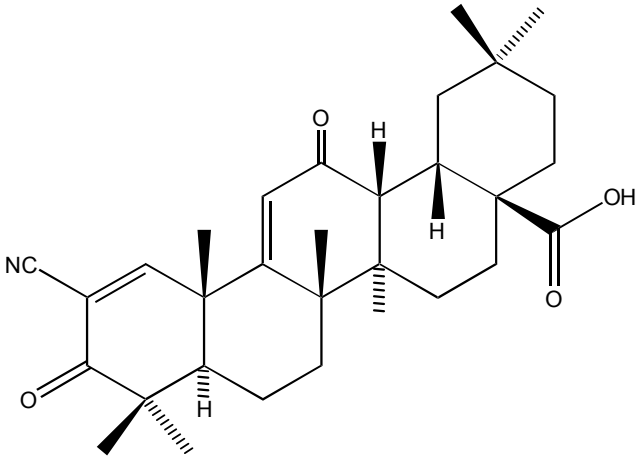


β-Lapachone

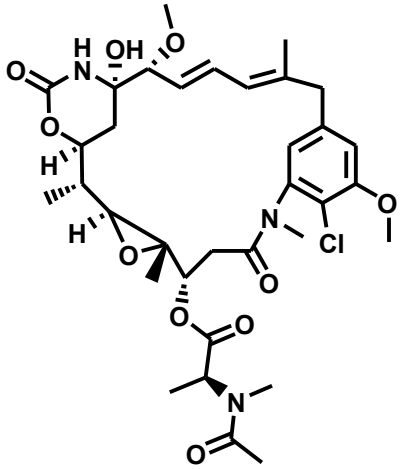


X = O Bromoindirubin
X = NOH Bromoindirubin oxime

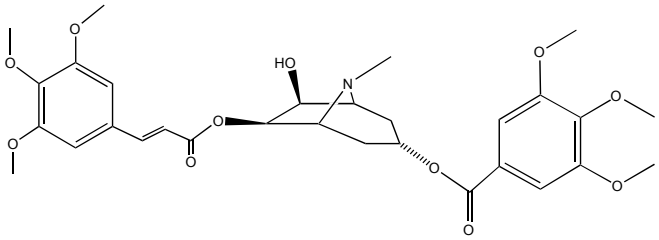
Figure 3: Plant-derived anticancer agents in various stages of pre-clinical development



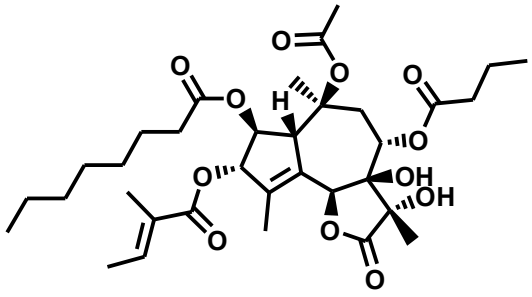
CDDO



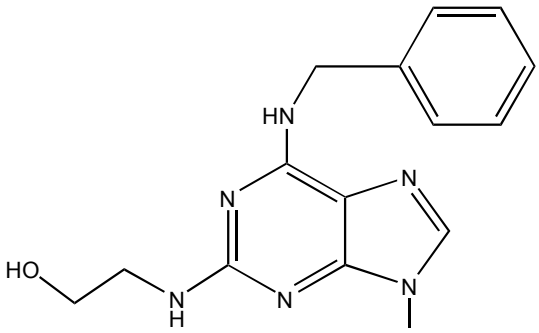
Maytansine



Pervilleine A



Thapsigargin



Olomucine

Figure 3 (Contd.): Plant-derived anticancer agents in various stages of pre-clinical development

(Erythroxylaceae) possess significant activity against MDR cancer (Mi et al., 2003).

Significance of cell cycle target inhibition in anticancer drug discovery

Initially the discovery of anticancer agents from natural sources depended on testing for cytotoxicity against cancer cell lines grown either *in vitro* or using *in vivo* models. Several naturally-obtained anticancer agents have shown to exert their cytotoxicity through interaction with tubulin. For example, VCR, VLB, colchicines, combretastatin and maytansine promote microtubule depolymerisation, whereas taxanes cause stabilization of microtubules against depolymerization. This unique mode of action of taxol aroused major interest in finding other molecules having similar mechanism and finally led to the isolation of a jatrophane ester (jatrophane 1) from *Euphorbia semiperfoliata* (Euphorbiaceae). Although earlier it was reported to be cytotoxic, later it was shown to act like paclitaxel (taxol) (Miglietta

et al., 2003). Epothilones are other taxol-like molecules obtained from microbial sources (Cragg and Newman, 2004).

Topotecan and irinotecan act through inhibition of topoisomerase I, involved in DNA winding/ unwinding. Other chemical entities having such mechanism of action are indenoquinolines and indenoisoquinolines and protoberberine alkaloid, nitidine, isolated from *Zanthoxylum* and *Fagara* species (Rutaceae) (Cragg and Newman, 2004). The flavonoids, quercetin, myricetin and flavopiridol have similar type of action.

Efforts on some other plant-derived anticancer molecules

Curcumin (diferuloylmethane) obtained from *Curcuma longa* (Indian saffron; Zingiberaceae) has been consumed by people for centuries as a dietary component and for a variety of proinflammatory ailments. It has the potential to sensitize tumors to different chemotherapeutic agents including paclitaxel, VCR, VLB, cisplatin, etoposide and vinorelbine. Chemosensitization has been observed in the cancers of breast, colon, pancreas, stomach (gastric), liver, blood, lung, prostate, bladder, ovary and brain and in multiple myeloma, leukemia and lymphoma. It also acts as a radiosensitizer for tumors. It also protects normal organs such as liver, kidney, oral mucosa and heart from chemotherapy- and radiotherapy-induced toxicity (Goel and Aggarwal, 2010).

Honokiol and magnolol, the main constituents of *Magnolia officinalis* (Magnoliaceae) have multiple pharmacological effects such as antitumor, antioxidant, antimicrobial, anti-inflammatory and antithrombotic effects (Fong et al., 2005; Chao et al., 2010). Honokiol, a small organic molecule has shown anticancer activities in a variety of cancer cell lines. It inhibits the growth and proliferation of oral squamous cell carcinoma (OSCC) and is promising for treatment in human OSCC (Chen et al., 2011). Magnolol inhibits human glioblastoma cell proliferation (Chen et al., 2009). *M. officinalis* may prove to be of considerable benefit in the prevention and treatment of bladder cancer (Lee et al., 2009). Magnolol, a hydroxylated biphenyl, suppresses metastasis via inhibition, migration, and matrix metalloproteinase-2/-9 activities in PC-3 human prostate carcinoma cells (Hwang and Park, 2010).

Evodiamine, a quinazolinocarboline alkaloid obtained from *Evodia rutaecarpa* (Rutaceae) has been found to be a dual catalytic inhibitor of type I and II topoisomerases and exhibits an enhanced inhibition against camptothecin-resistant cells (Pan X et al., 2012). Evodiamine exhibited selective antitumor and antimetastatic effects on several cancer cell lines and became lead structure of anticancer agents (Bubenyák, 2011). The phenanthridine type alkaloid, ungeremine, isolated from *Pancratium illyricum* (Amaryllidaceae), effectively targets mammalian as well as bacterial type I and II topoisomerases (Casu et al., 2011).

The carbazole alkaloid, grinimbine, isolated from edible herb, *Murraya koenigii* (Rutaceae), inhibited the growth and induced apoptosis in human hepatocellular carcinoma, HepG2 cells. It may be promoted for use as an anticancer agent against hepatocellular carcinoma (Syam et al., 2011). Brucine, a natural plant alkaloid, is reported to possess cytotoxic and antiproliferative activities (Agrawal et al., 2011). The phenanthroindolizidine alkaloid, S-(+)-deoxytylophorinidine, isolated from *Tylophora ovata* (Apocynaceae) and *T. atrofolliculata* displayed potent anticancer activity *in vitro* and *in vivo* (Liu et al., 2011a). Sanguinarine, a benzophenanthridine alkaloid, obtained primarily from the bloodroot plant suppresses prostate tumor growth and inhibits survivin expression. Sanguinarine may be developed as an agent either alone or in combination with taxol for the treatment of prostate cancer overexpressing survivin (Sun et al., 2010). Narciclasine, isolated from *Narcissus pseudonarcissus* (Amaryllidaceae), displayed potent inhibitory activity to human CYP3A4 whereas trans-dihydronarciclasine is a readily available molecule with potent and selective anticancer activity (McNulty et al., 2011).

Pentopetia androsaemifolia (Apocynaceae) provided ipomoeassin F, which showed promising antiproliferative action (Adou et al., 2010). Berberine, an isoquinoline alkaloid, present in *Mahonia baelei* (Berberidaceae) exhibited strong antiproliferative

action on HT-29 cells (Hu et al., 2011). Berberine and sanguinarine possess nucleic acid binding properties, which can be interpreted in relation to their anticancer activity. Stemona alkaloid, stemofoline, isolated from *Stemona aphylla* (Stemonaceae), showed synergistic growth inhibitory effect with cancer chemotherapeutic agents including VLB and paclitaxel. It may be effective in the treatment of multidrug-resistant cancer and could be a new potential MDR chemosensitizer (Chanmahasathien et al., 2011). Mahanine, isolated from *Murraya koenigii* showed antiproliferative activity in acute lymphoid (MOLT-3) and chronic myeloid (K562) leukemic cell lines (Bhattacharya et al., 2010).

Goniotriol, (+)-altholactone, (+)-goniofufrone and the aporphine alkaloid, (-)-nordicentrine, isolated from *Goniothalamus laoticus* (Annonaceae), showed toxicity against cancer cells - KB, BC1, NCI-H187, and MCF-7 (Lekphrom et al., 2009). Amaryllidaceae alkaloids, narciclasine, lycorine, and haemanthamine have been reported to possess apoptosis-inducing properties. The antiinvasive activity of buphanamine is promising because this alkaloid is not toxic to cells even at much higher doses (Evidente et al., 2009). NSC 338 258 (EPED3), a highly stable hydrophilic derivative of the alkaloid, ellipticine, exhibited dramatic cytotoxic activity against myeloma cells. It targets mitochondrial function to rapidly deplete chemical energy and initiate apoptosis in myeloma cells at nanomolar concentrations while leaving stromal cells unharmed (Tian et al., 2008).

Matrine, a component of *Sophora flavescens* (Fabaceae), possesses strong antitumor activities *in vivo* and *in vitro* against murine hepatocellular carcinoma H22 cells. Inhibition of cell proliferation and induction of apoptosis are the likely mechanisms responsible for its antitumor activities (Ma et al., 2008). Sodium pancratistatin 3,4-*O*-cyclic phosphate is a novel water soluble synthetic derivative of pancratistatin, a natural alkaloidal constituent of Amaryllidaceae plants that exhibits good cytostatic and antineoplastic activity but is highly insoluble (Shnyder et al., 2008). Piperlonguminine, an amide alkaloid has been obtained from peppers, including *Piper divaricatum* (Piperaceae). It displayed *in vivo* growth inhibition of sarcoma 180 (Bezerra et al., 2008). A benzophenanthridine alkaloid, rutaceline, isolated from *Zanthoxylum madagascariense* (Zygophyllaceae) indicated higher cell growth inhibition on the colon adenocarcinoma cells (Pachon et al., 2007). A novel anticancer drug amitosine representing the mixture of thiophosphamide-modified alkaloids from *Chelidonium majus* (Papaveraceae) has been reported to inhibit growth of various solid tumors *in vivo*. Amitosine has been shown to possess strong antiproliferative and apoptosis-inducing activities in MT-4 cells *in vivo*, which seem to be mediated partially through caspase-dependant mitochondrial death pathways (Fil'chenkov et al., 2006).

The acridone alkaloids – arborinine and evoxanthine, isolated from *Ruta graveolens* (Rutaceae), inhibited the proliferation of human cell lines HeLa, MCF7 and A431. Naturally occurring furanoacridones can be regarded as excellent starting structures for the potential development of new anticancer agents (Réthy et al., 2007). Coramsine is a novel chemotherapeutic agent isolated from *Solanum linnaeanum* (Devil's Apple; Solanaceae). Systemic administration of coramsine slowed tumor growth and prolonged survival time (van der Most et al., 2006). Dihydronitidine isolated from *Toddalia asiatica* (Rutaceae) had highly specific cytotoxicity to human lung adenocarcinoma (A549) cells. It manifested its characteristics in the tumor selective toxicity, contrasting with the case of a known anticancer agent camptothecin (Iwasaki et al., 2006). 1,7-Deoxy-4-deacetylbaccatin III and some of its analogs showed significant activity as MDR reversal agent by the assay of the calcein accumulation towards MDR human ovarian cancer 2780AD cells (Hasegawa et al., 2007). Sampangine is a copyrine alkaloid obtained from the stem bark of *Cananga odorata* (Annonaceae). This azaoxoaporphine alkaloid is cytotoxic to human malignant melanoma cells. Azaoxoaporphine alkaloids can be a lead for the design of pro-apoptotic anticancer agents (Kluza et al., 2005). *Silybum marianum* (Milk thistle;

Asteraceae) is one of the most commonly used herbal therapies and its principal constituent silybin inhibits cytochrome P450 isoform 3A4 (Cyp3A4) and UDP glucuronosyltransferase isoform 1A1 (UGT1A1) *in vitro*. Effect of milk thistle on the pharmacokinetics of irinotecan was studied and it was found that the concentration of silybin was too low to affect the function of these enzymes (van Erp et al., 2005).

Ukrain® is an anticancer drug based on the extract of the plant *Chelidonium majus* (Papaveraceae). It is semisynthetic derivative of chelidonine. Numerous preclinical and clinical investigations suggested it to be pharmacologically active and clinically effective. The data from randomized clinical trials suggested Ukrain® to have potential as an anticancer drug (Ernst and Schmidt, 2005). Chelidonine turned out to be a potent inducer of apoptosis triggering cell death (Habermehl et al., 2006). Cepharanthine is a plant alkaloid that effectively reverses resistance to anticancer agents. Cepharanthine enhanced sensitivity to doxorubicin (ADM) and vincristine (VCR) and enhanced apoptosis induced by ADM and VCR of p-gp negative K562 cells. Cepharanthine in combination with ADM should be useful for treating patients with tumors (Ikeda et al., 2005). Glycoalkaloids delta tomatine, solamargine, solasonine and jervine obtained from potato, tomato and egg plant were found to be more potent against the liver carcinoma cells than doxorubicin and camptothecin (Lee et al., 2004). Ellipticine was isolated from Australian evergreen tree of Apocynaceae family. Its planer polycyclic structure was found to interact with DNA through intercalation, indicating a high DNA binding affinity. The presence of protonatable ring nitrogens distinguished ellipticine from other simple intercalators (Garbett and Graves, 2004). The potent ellipticine derivative, 6-propanamine ellipticine induced rapid apoptosis in MDA-MB-231 breast cancer cells. Induction of endoplasmic reticulum stress may contribute to the cytotoxicity of ellipticines (Hägg et al., 2004). Originally isolated from an Australian plant, acronycine is an antitumor alkaloid with poor water solubility and low potency. The modest antitumor activity was markedly improved by the synthesis of analogs, a diester derivative of 1,2-dihydrobenzo[b]acronycine. The molecular mechanism of action of this compound could involve DNA alkylation, modulation of cyclin E protein levels and inhibition of DNA synthesis leading to apoptosis (Guilbaud et al., 2002).

Harringtonine, homoharringtonine and isoharringtonine are cephalotaxine alkaloids with anticancer activities, which were isolated from *Cephalotaxus hainanensis* (Taxaceae) indigenous to China. The cytotoxicity of isoharringtonine paralleled with cell apoptosis and indicated that the anticancer activity results from the induction of apoptosis (Shi and Han, 1998). Hyperforin, an antibiotic from *Hypericum perforatum* (St. John's Wort; Hypericaceae) inhibits the growth of tumor cells by induction of apoptosis. Hyperforin activates a mitochondria-mediated apoptosis pathway and is of interest because of low toxicity *in vivo* (Schempp et al., 2002).

Cryptolepine and neocryptolepine are two indoloquinoline alkaloid derivatives isolated from the roots of African plant *Cryptolepis sanguinolenta* (Apocynaceae). These two alkaloids intercalate into DNA and interfere with the catalytic activity of human topoisomerase II (Dassonneville et al., 2000). Voacangine, voacamine and epivoacarine, isolated from *Tabernaemontana arborea* (Apocynaceae) were the major cytotoxic constituents against P-388 lymphocytic leukemia (Kingston, 1978). Gabunine and 19-(2-oxopropyl) conodurine, isolated from *T. holstii* displayed significant inhibitory activity against P-388 cell culture (Kingston et al., 1977).

Retrosine is a member of the pyrrolizidine alkaloid family of naturally occurring compounds found in a large number of plant species worldwide. Bioactivation of pyrrolizidine alkaloids by liver cytochrome P450 (CYP) enzymes is required for their toxicity. Studies demonstrated enhanced or induced expression of hepatic CYP's in response to retrosine exposure in rats (Gordon et al., 2000). The phenanthroindolizidine alkaloids pergularinine (PGL) and tylophorinidine (TPD) isolated from Indian herb *Pergularia pallida* (Apocynaceae) were subjected to cytotoxicity studies. Both the alkaloids

significantly inhibited dihydrofolate reductase (DHFR) activity. Concentrations greater than 75-95 microM resulted in a complete loss of DHFR activity suggesting their potential as antitumor agents (Rao and Venkatachalam, 2000). (+)-(13aS) Deoxytylophorinine, isolated from *Tylophora atrofolliculata* (Apocynaceae) and *T. ovata* exerts both *in vitro* and *in vivo* anticancer activities and can have sequence-specific interactions with DNA in intercalating manner (Liu et al., 2011b).

Sanguinarine obtained from the bloodroot plant *Sanguinaria canadensis* (Papaveraceae) exhibited anticancer properties. Sanguinarine induces apoptosis of H-29 human colon cancer cells. It significantly increases the activation of caspases 3 and 9 that are the key executioners in apoptosis (Lee et al., 2012). Solamargine, a major steroidal alkaloid glycoside has been isolated from *Solanum nigrum* (Solanaceae). Solamargine exerted potential anticancer activity on SMMC-7721 cells *in vitro* through the activation of caspase-3 and regulation of the cell cycle progression to induce apoptosis and inhibit hepatoma cell proliferation (Ding et al., 2012).

An antitussive alkaloid, noscapine binds tubulin, displays anticancer activity and has a safe pharmacological profile in humans. The analog of noscapine, 9-nitro-noscapine binds tubulin and induces apoptosis selectively in ovarian and T-cell lymphoma resistant to paclitaxel, vinblastine, and teniposide. This analog has a great potential to be a novel therapeutic agent for ovarian and T-cell lymphoma cancers, even those that have become drug-resistant to currently available chemotherapeutic drugs (Aneja et al., 2006). Thiocolchicoside, a semisynthetic colchicoside from *Gloriosa superba* (Colchicaceae), is a muscle-relaxant and used to treat rheumatologic and orthopaedic disorders because of its analgesic and anti-inflammatory mechanism. Thiocolchicoside inhibited proliferation of leukemia, myeloma, squamous cell carcinoma, breast, colon and kidney cancer cells. It also suppresses formation of tumor colonies and exhibits anticancer activity through inhibition of NF-kB and NF-kB-regulated gene products (Reuter et al., 2010).

Vallesiachotamine, sewarine and tetrahydrosecamine isolated from *Rhazya stricta* (Apocynaceae) displayed cytotoxic activity. Tetrahydrosecaminediol was highly toxic (Mukhopadhyay et al., 1981). Several quassinoids were isolated from *Simaba multiflora* (Simaroubaceae). 6-Alpha-senecioyloxyc haparrinone displayed activity against KB and P-388 test systems (Arisawa et al., 1983a). *S. multiflora* provided 10-methoxycanthin-6-one and 10-hydroxycanthin-6-one showing cytotoxic properties (Arisawa et al., 1983b). Reserpine, the active substance isolated from *Rauvolfia serpentina* (Apocynaceae) possesses antihypertensive, tranquilizing and vasodepressor activity. It was employed as supportive therapy in the treatment of cardiac disorders. Doxorubicin is a potent anticancer agent, the use of which is limited by its cumulative dose-dependant cardiotoxicity. Epirubicin is a derivative of doxorubicin. Reserpine acts as a chemosensitizer, when used in combination with epirubicin on P-388 murine leukemia cells sensitive and resistant to doxorubicin. Reserpine can be used as an adjuvant in the cancer chemotherapy to potentiate the antiproliferative action of anticancer drugs (Viladkar and Chitnis, 1993).

Pancratistatin isolated from *Pancratium maritimum* (Amaryllidaceae) is now undergoing preclinical development as an anticancer agent. It has also been isolated from *Hymenocallis speciosa* (Amaryllidaceae) (Singapore), *H. variegata* (Singapore), *H. pedalis* (Seychelles), *H. expansa* (Bermuda), *H. sonorensis* (Mexico) (Pettit et al., 1995). Echitamine chloride, an indole alkaloid isolated from the bark of *Alstonia scholaris*, has been reported to have a highly promising anticancer activity against fibrosarcoma in rats. Echitamine chloride affects both cellular and mitochondrial respiration leading to reduction of the cellular energy pool and thereby resulting in the loss of viability of S-180 cells (Saraswathi et al., 1998).

Beta-carboline alkaloid, harmine, has been isolated from *Peganum harmala* (Nitrariaceae). This plant is reported to be used as folk medicine in anticancer therapy. Several derivatives of

harmine were prepared. Administration of these compounds resulted in tumor inhibition in mice bearing Lewis Lung cancer, sarcoma 180 or HepA tumor (Chen et al., 2005). Deoxytubulosine (DTB) isolated from *Alangium lamarckii* (Cornaceae) was demonstrated to possess potent cytotoxicity. This beta-carboline-benzoquinolizidine alkaloid displayed dihydrofolate reductase and cell growth inhibitory activity (Rao and Venkatachalam, 1999). Harmine, harmane, harmaline, harmalol and tryptoline isolated from *P. harmala* were investigated for binding with RNA. The affinity of alkaloids-RNA binding was in the order of harmine > harmaline > harmane > harmalol > tryptoline (Nafisi et al., 2010). Harmine may be a strong angiogenic inhibitor with the ability to decrease the proliferation of vascular endothelial cells and to reduce expression of various pro-angiogenic factors (Hamsa and Kuttan, 2010). Harmol induces apoptosis by caspase-8 activation independently from Fas/Fas ligand interaction in human non-small cell lung cancer H-596 cells. It induces cell death via autophagy (Abe et al., 2011).

The chemomodulatory activity of *Alstonia scholaris* (Apocynaceae) extract was studied in combination with berberine hydrochloride, a topoisomerase inhibitor, in Ehrlich ascites carcinoma-bearing mice. It was effective when administered in the early stages but the efficiency decreased with an increase in the tumor developmental stages (Jagetia and Baliga, 2004). Berberine is a protoberberine alkaloid widely distributed in the species of *Berberis*. Berberine exerts anticancer activities both *in vivo* and *in vitro* through different mechanisms. It showed inhibitory effects on the proliferation and reproduction of certain tumorigenic microorganisms and virus, such as *Heliobacter pylori* and hepatitis B virus. Berberine is a broad spectrum enzyme inhibitor, which affects N-acetyltransferase, cycloxygenase-2 and topoisomerase activities and gene / protein expression. The suppression of tumor growth and metastasis, the beneficial application in combined medication, and the improvement of multidrug resistance both *in vivo* and *in vitro* clearly show its potential as an alternative medicine for chemotherapy (Sun et al., 2009). Berbamine has been isolated from *Berberis amurensis*. It has been reported to possess antileukemic activity. Its anticancer activity against human hepatocellular carcinoma, HepG2 cells *in vivo* and *in vitro* was studied. The treatment decreased the cell growth in a dose-dependant manner (Wang et al., 2009). It has been shown that berberine induces apoptosis in acute lymphoblastic leukemia cells by down regulating the MDM2 oncoprotein (Zhang et al., 2010). The antiangiogenic activity of berberine is mainly mediated through the inhibition of various proinflammatory and pro-angiogenic factors and the major ones are proinflammatory cytokines, hypoxia-inducing factors and vascular endothelial growth factor (Hamsa and Kuttan, 2012).

Effects of some triterpenoids from *Panax* and *Glycyrrhiza* spp. on the sensitivity to daunomycin and vinblastine of adriamycin (ADM)-resistant P388 leukemia cells, which were resistant to multiple anticancer drugs, were examined *in vitro*. Quasipanaxatriol, 20(S)-protopanaxatriol, ginsenoside Rh2 greatly enhanced the cytotoxicity of the anticancer drugs in P-388 / ADM cells. The maximum increase in cytotoxicity was observed with quasipanaxatriol (Hasegawa et al., 1995). Parthenolide is an active sesquiterpene lactone present in a variety of medicinal herbs. It exerted *in vitro* stimulatory activity on tubulin assembly, by inducing the formation of well-organized microtubule polymers. Combined treatment of parthenolide and paclitaxel in human breast cancer MCF-7 cells demonstrated significant inhibition of growth. The antimicrotubular and antiproliferative effects of parthenolide may influence paclitaxel activity. The tubulin / microtubule system may represent a novel molecular target for parthenolide, to be utilized in developing new combinatorial anticancer strategies (Miglietta et al., 2004).

Asiatic acid is a pentacyclic triterpene found in medicinal plants. The cytotoxic effect of this compound and its augmentative effect on anticancer drug irinotecan hydrochloride (CPT-11) were investigated in human colon adenocarcinoma cell line HT-29. Asiatic acid induced apoptosis in HT-29 cells via caspase-3 activation. Combined treatment of parthenolide and CPT-11 showed

additive effect. Synergism was observed when cells were first exposed to CPT-11 and then to asiatic acid. Asiatic acid can be used as an agent for increasing sensitivity of colon cancer cells to treatment with CPT-11 or as an agent for reducing adverse effects of CPT-11 (Bunpo et al., 2005). Triptolide, celastrol and tripchlorolide isolated from *Tripterygium wilfordii* showed anticancer activity. This plant is used in China for the treatment of immunological disorders since ancient times. Triptolide derivatives with improved water solubility have emerged as promising drug candidates. They exert their actions by modulating the transcriptional activity of nuclear factor-kB signalling molecule (Wong et al., 2012).

The effects of dietary phytochemicals on the functions of p-glycoprotein and MRP1 were studied. Glycyrrhetinic acid (GA) found in *Glycyrrhiza glabra* (Fabaceae) increased the accumulation of calcein, a fluorescent substrate of MRP1, in KB / MRP cells. KB / MRP and KB / C2 cells were sensitized to cancer drugs by GA, showing that it reverses multidrug resistance. GA also stimulated the ATPase activity of MRP-1. Since GA have dual inhibitory effects on p-glycoprotein and MRP1, it may be useful to enhance the efficacy of cancer chemotherapy (Nabekura et al., 2008). The flavonoid, oroxylin A, isolated from the roots of *Scutellaria baicalensis* (Lamiaceae) increased the cellular accumulation of calcein AM in a concentration-dependant manner in NC1/ADR-RES cells overexpressing p-glycoprotein. Cancer cells become more susceptible to the cytotoxicity of vinblastine and paclitaxel in the presence of oroxylin A. Oroxylin A was effective in inhibiting p-glycoprotein-mediated drug efflux both *in vivo* and *in vitro*, suggesting that it may be useful to improve the cellular availability of p-glycoprotein substrate such as anticancer drugs (Go et al., 2009).

Two cucurbitacin derivatives, dihydrocucurbitacin B and cucurbitacin B, isolated from *Cucumis prophetarum* (Cucurbitaceae) were tested towards human cancer cell lines, mouse embryonic fibroblast (NIH3T3) and virally transformed form (KA3IT). These are leads for discovering new anticancer drugs (Ayyad et al., 2011). Several naphthoquinone derivatives (arnebin 1 to arnebin 7) were isolated from the roots of *Arnebia nobilis* (Lamiaceae) (Shukla et al., 1969; 1971; 1973). The wound healing property of *A. nobilis* is known from ancient Arabian literature. The anticancer activity of this plant was associated with arnebin-1 (Alkannin β, β-dimethyl acrylate) and arnebin-3 (alkannin acetate). Both these compounds showed promising activity against Walker carcinosarcoma 256 in rats but poor solubility and toxicity affected further work on them (Gupta and Mathur, 1972). The furanoxanthone, psorospermin obtained from Guttiferae is highly promising, exhibiting significant cytotoxicity through a novel mechanism of action, being an irreversible topoisomerase II poison (Pouli and Marakos, 2009).

Crude extract of some plants displayed promising anticancer activity. *Onosis hirta* (Fabaceae) and *Inula viscosa* (Asteraceae) exerted their antiproliferative activity by inducing apoptosis in cancer cell lines (Talib and Mahasneh, 2010). Cytotoxic effect of the *Beta vulgaris* (red beetroot; Chenopodiaceae) was compared with anticancer drug doxorubicin (adriamycin) in the androgen-independent human prostate cancer cells (PC-3) and in the well established estrogen receptor-positive human breast cancer cells (MCF-7). Both doxorubicin and beetroot extract exhibited a dose-dependant cytotoxic effect in the two cancer cell lines tested (Kapadia et al., 2011). *Coptis chinensis* (Ranunculaceae) induced tumor cell inhibition. It may be a novel therapeutic drug for squamous cell carcinoma (Wang et al., 2011).

The activity of *Uncaria tomentosa* (Rubiaceae) was studied in cancer cells using *in vivo* and *in vitro* models. The preparations were non-toxic and well tolerated (Pilarski et al., 2010). The methanolic extract of *Foeniculum vulgare* (fennel; Apiaceae) seeds was studied for cytotoxic and antitumor activities. It may have remarkable anticancer potential against breast (MCF7) and liver (Hepg2) cancer cell lines. It exhibited an antitumor effect by modulating lipid peroxidation and augmenting the antioxidant defense system in Ehrlich ascites carcinoma-bearing mice with or without exposure to radiation (Mohamad et al., 2011). *In vitro*, total

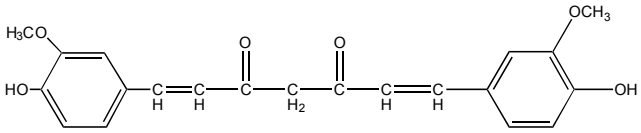
alkaloid fraction of *Viscum coloratum* (Viscaceae) shows prominent inhibitory effect on the growth of carcinoma cells. *In vivo*, it shows that total alkaloid can inhibit the growth of tumors and prolong the survival days of the mice bearing tumors (Peng et al., 2005). *Trichosanthes kirilowii* (Cucurbitaceae) tuber extract (TKE) was investigated for anticancer properties. The treatment moderately affected alpha-tubulin protein production, but not that of beta-tubulin and its gene expression. Anticancer mechanism of TKE was linked to the inhibition of tubulin polymerization, through which it exerts cell cycle arrest at the G2 / M phase in the HepG2 cell line (Shin et al., 2008).

The whole plant of *Sedum sarmentosum* (Crassulaceae) has been traditionally used in China and South Korea for the treatment of chronic viral hepatitis. Crude alkaloid fraction of *S. sarmentosum* caused a dose-dependant inhibition of cell proliferation without necrosis or apoptosis. It was suggested that *S. sarmentosum* may improve survival of hepatoma patients via the inhibition of excessive growth of tumor cells (Kang et al., 2000). Leaf extracts of *Calotropis gigantea* (Apocynaceae) and *Vallaris glabra* (Apocynaceae) showed great promise as potential candidates for anticancer drugs (Wong et al., 2011).

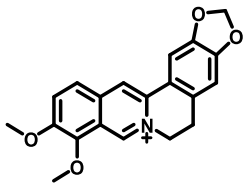
Berberis aristata (Berberidaceae) is used by herbal healers to treat cancer. Ethanol extract was found to be more efficient and flavonoids and alkaloids may be responsible for the anticancer effects (Pai et al., 2012). The methanolic extract of *Teucrium polium* (Lamiaceae) (Me-Tp) showed promoting effect on the cytotoxic and apoptotic activity of anticancer drugs – vincristine, vinblastine and doxorubicin *in vitro*. The studies suggest that Me-Tp has the potential to be an effective and safe chemosensitizer for cancer therapy (Rajabalian, 2008). *Retama monosperma* (Fabaceae) extract exhibits a potential anticancer activity against cervical cancer cell lines *in vitro* through the inhibition of proliferation and induction of apoptosis, which may involve a mitochondria-mediated signaling pathway (Merghoub et al., 2011). The anticancer effect of alkaloid fraction of *Alstonia scholaris* (Apocynaceae) was studied *in vitro* in cultured human neoplastic cell lines (HeLa, HL60, KB and MCF-7) in Ehrlich ascites carcinoma. The effect of alkaloid fraction was better than cyclophosphamide which was used as positive control (Jagetia and Baliga, 2006). Benzophenones from *Anemarrhena asphodeloides* have been found to show anticancer activity in HepG2 cells via the NF-êB signaling route (Wu et al., 2019). Melosuavine I is a bisindole alkaloid isolated from the leaves of *Melodinus suaveolens* that has been found to possess apoptosis-inducing property (Fang et al., 2019). Gomisin J from *Schisandra chinensis* fruit has been found to have anticancer activity (Jung et al., 2019). Baicalin, a major flavonoid isolated from the roots of the traditionally used Chinese plant *Scutellaria baicalensis*, has been found to induce colon cancer cell apoptosis through inhibition of oncomiRNAs (Tao et al., 2018). Among the various types of plant phenolic compounds like flavonoids, lignans, tannins, phenolic acids, xanthones, stilbenes, curcuminoids, coumarins, etc, the lignans are most promising for cancer prevention and treatment (Teodor et al., 2020).

Biosynthesis of novel phytomolecules and novel activities for known phytomolecules

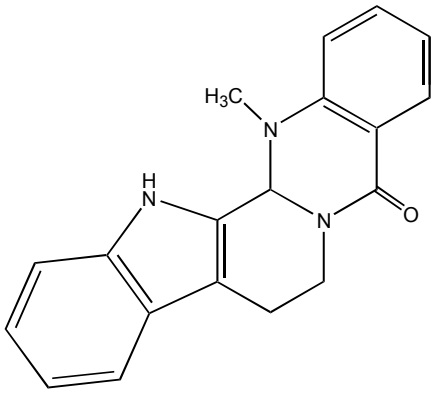
Recently some known phytomolecules have been given a re-look to elucidate their potential anticancer activity. One recent example is that of L-menthol, a naturally occurring cyclic monoterpene obtained from *Mentha arvensis* (Lamiaceae) that has been traditionally used in oral hygiene products, confectionery, cosmetics and as a flavouring agent. An omics approach indicated that L-menthol modulates tubulin polymerization and apoptosis to inhibit human epithelial colorectal adenocarcinoma cell proliferation (Faridi et al., 2011; 2016). Similarly, Puerarin (Pue), belonging to the isoflavone glycoside group and derived from *Pueraria lobata*, *P. thomsonii* and *P. tuberosa* was recommended by the Chinese Health Ministry for treating various ailments in 1993, but later it was found to possess anticancer activity too by virtue of it being an inducer of apoptosis (Ahmad et al., 2020). In traditional Chinese medicine sesquiterpene lactones have been used for treating



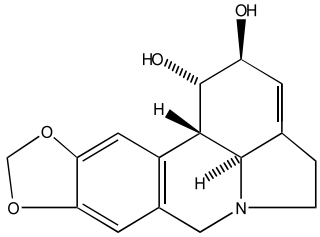
Curcumin



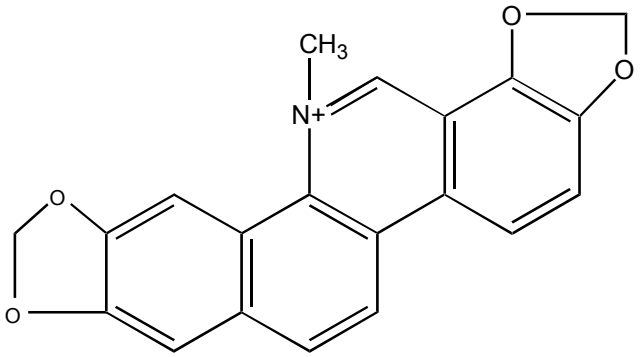
Berberine



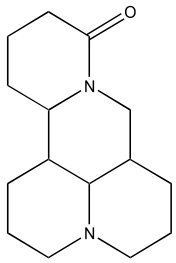
Evodiamine



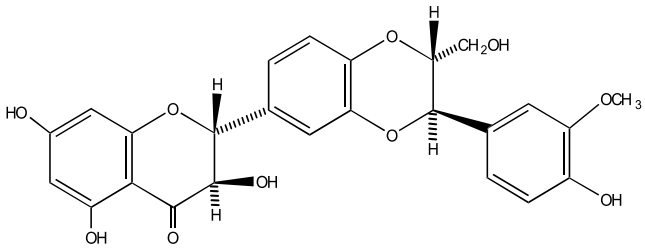
Lycorine



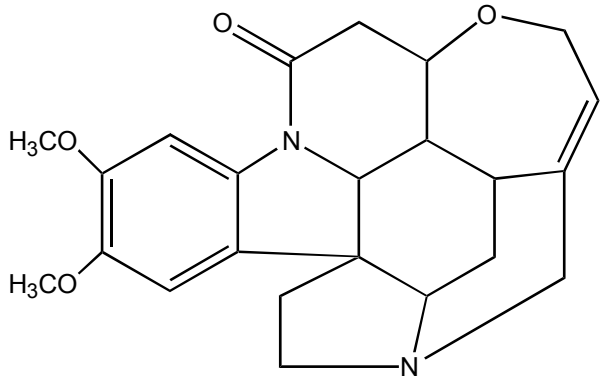
Sanguinarine



Matrine

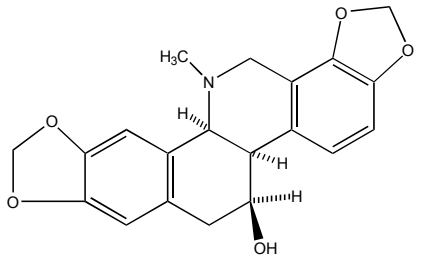


Silybin

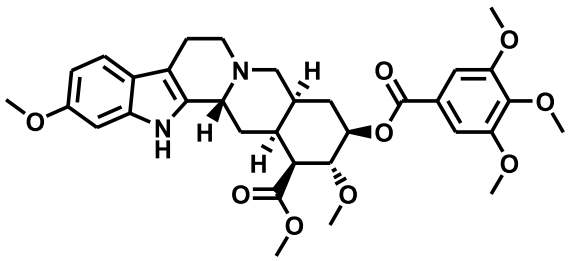


Brucine

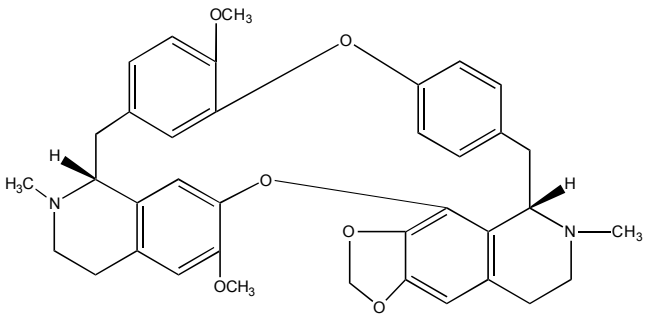
Figure 4: Some potential plant-derived anticancer molecules under active research scrutiny in recent times



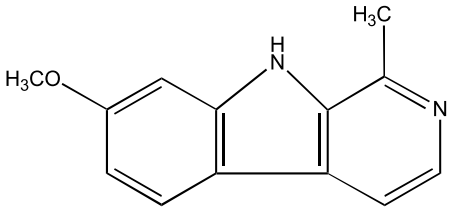
Chelidonine



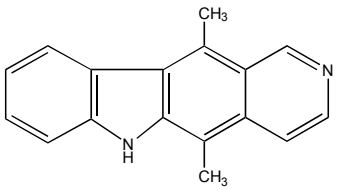
Reserpine



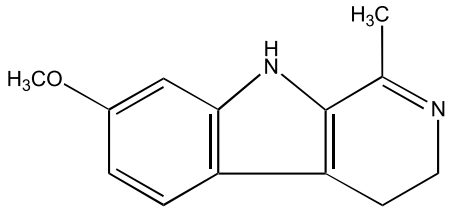
Cepharanthine



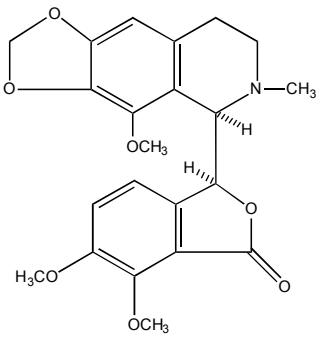
Harmine



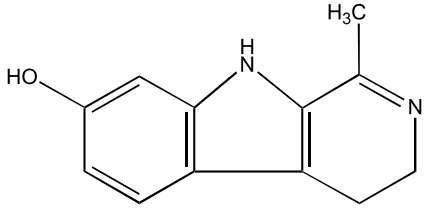
Ellipticine



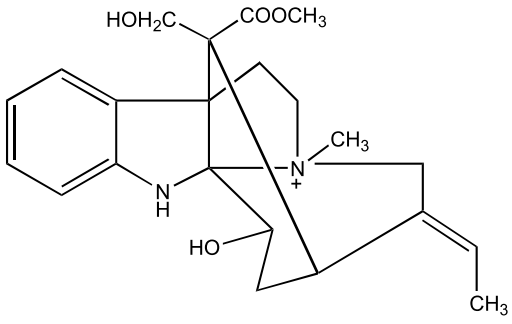
Harmaline



Noscapine

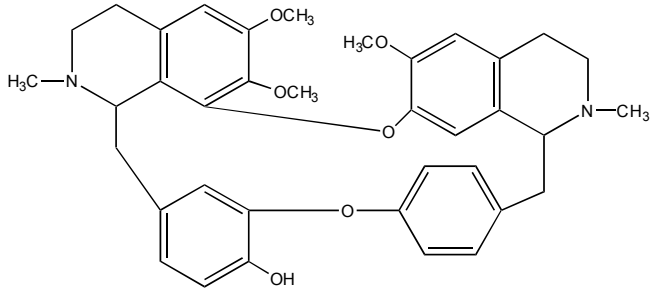


Harmalol

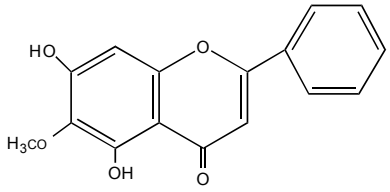


Echitamine

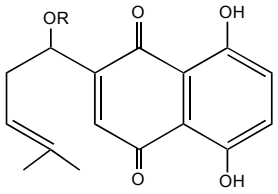
Figure 4 (Contd.): Some potential plant-derived anticancer molecules under active research scrutiny in recent times



Berbamine



Oroxylin A



R = β, β-Dimethylacrylate Arnebin-1
R = Acetate Arnebin-3

Figure 4 (Contd.): Some potential plant-derived anticancer molecules under active research scrutiny in recent times

inflammatory diseases but recently they have also been shown to possess anticancer activity (Mehmood et al., 2017). Santamarine is a type of sesquiterpene lactone, which has been shown to possess anticancer activity (Jalal et al., 2020).

Another interesting development has been the green approach of "Metabolic Reprogramming" of plant biosynthetic pathways to produce novel / unusual structures possessing novel activities. This approach has been applied in the case of terpenoid indole alkaloid (TIA) biosynthetic pathway in *C. roseus*. The study of precursor-directed biosynthesis in *C. roseus* has revealed that one key bottleneck in the production of unnatural alkaloids is the stringent substrate specificity of strictosidine synthase, the enzyme that catalyzes formation of the biosynthetic intermediate strictosidine from secologanin and tryptamine. Design of enzyme mutants with broadened substrate specificities allows enzymatic production of a greater variety of strictosidine analogs (Runguphan and O'Connor, 2009). RNA silencing of tryptophan decarboxylase suppresses the biosynthesis of tryptamine in *C. roseus* and in such a scenario exogenously providing tryptamine analogs like 5-fluorotryptamine leads to unnatural, fluorinated alkaloids (Runguphan et al., 2009). Integration of carbon–halogen bond formation into *C. roseus* metabolism has also been attempted to yield novel alkaloid structures (Runguphan et al., 2010). Screening of such unusual structures could probably provide a greener approach to new anticancer drug development.

Traditional knowledge as the basis for selection of medicinal plants for tackling cancer

Traditional systems of medicine like Ayurveda have been practiced since ancient times (since ~1000 B.C) (Shukla et al., 2013). Plant-based drugs (*Audbhid*) find an important place in Ayurveda. The complexity that needs to be tackled is that many of the modem day diseases (including cancer) need to be correlated to Ayurveda based on their symptoms mentioned in Ayurveda since they were described by different names in ancient Ayurvedic texts. Three disease conditions mentioned in Ayurveda possibly correlate with modem day description of cancer. These are namely, *Arbuda*, *Granthi* and *Gulma*. Logically, plants recommended for curing these three would have higher probability of hit rates in anti-cancer drug discovery (**Table 1**). Since Ayurveda follows a holistic approach for preventive / curative disease management, these selected plants may also possess alternative therapeutic properties apart from anticancer activity. As per Ayurveda, in benign neoplasms (*Vataja, Pittaja or Kaphaja*) one or two of the three bodily systems are out of balance and it is not fatal as the body is still trying to coordinate a balance among them. On the contrary, malignant tumours (*Tridosaja*) are fatal as all the three major bodily systems lose mutual coordination and it results in a deadly morbid condition (Jain et al., 2009). Some compound Ayurvedic formulations like *Kanchnar guggulu* are used clinically for the treatment of benign and malignant tumors (Tomar et al., 2018).

Table 1: Plants recommended in Ayurveda for curing diseases (*Arbuda*, *Granthi* and *Gulma*) having cancer-like symptoms

S. No.	Botanical name	Common name	Plant part prescribed for use	Family
1	*Ailanthus excelsa*	Tree of heaven	Root bark	Simaroubaceae
2	*Albizia lebbeck*	Siris	Stem bark	Fabaceae
3	*Albizia procera*	White siris	Bark	Fabaceae
4	*Alstonia scholaris*	Milkwood pine, Blackboard tree	Stem bark	Apocyanaceae
5	*Aphanamixis polystachya*	Pithraj tree	Bark, roots	Meliaceae
6	*Araucaria cunninghamii*	Hoop pine, Dorrigo pine	Whole plant	Araucariaceae
7	*Aristolochia indica*	Indian birthwort	Aerial parts	Aristolochiaceae
8	*Basella rubra*	Ceylon spinach	Leaves and stem	Basellaceae
9	*Butea monosperma /Butea frondosa*	Palas, Flame-of-the-forest	Flowers	Fabaceae
10	*Caesalpinia sappan*	Indian redwood	Heartwood	Fabaceae
11	*Cassia fistula*	Amaltās, Golden-rain	Seed	Fabaceae
12	*Casuarina equisetifolia*	Jungli Saru	Stem bark	Casuarinaceae
13	*Cedrus deodara*	Devadāru	Stem wood	Pinaceae
14	*Ceratonia siliqua*	Carob	Germ flour	Fabaceae
15	*Cinnamomum camphora*	Camphor tree	Wood	Lauraceae
16	*Codiaeum variegatum*	Garden croton	Leaves	Euphorbiaceae
17	*Delonix regia*	Gulmohar	Flowers	Fabaceae
18	*Ehretia laevis*	Chamror	Fruits	Ehretiaceae
19	*Elaeocarpus ganitrus*	Rudraksha	Bark	Elaeocarpaceae
20	*Erythrina variegata*	Pārijāta	Leaves	Fabaceae
21	*Eucalyptus tereticornis*	Forest red gum	Leaves	Myrtaceae
22	*Ficus carica*	Common fig	Fruit, resin	Moraceae
23	*Ficus religiosa*	Peepal, Sacred fig	Bark	Moraceae
24	*Ficus rumphii*	Rumpf's Fig	Leaves	Moraceae
25	*Gardenia jasminoides*	Gandhraj, Cape jasmine	Fruit	Rubiaceae
26	*Gmelina asiatica*	Badhara bush, Asian bushbeech	Aerial parts	Lamiaceae
27	*Heterophragma adenophyllum*	Marodphali	Leaves and seeds	Bignoniaceae
28	*Hibiscus rosa-sinensis*	Gudhal, China rose	Aerial parts	Malvaceae
29	*Jatropha integerrima*	Spicy jatropha	Aerial parts	Euphorbiaceae
30	*Grewia asiatica*	Phalsa	Bark	Malvaceae
31	*Kigelia africana*	Cucumber tree	Fruit and bark	Bignoniaceae
32	*Kleinhovia hospita*	Bhola	Leaves	Malvaceae
33	*Lagerstroemia reginae*	Queen's crepe	Leaves	Lythraceae
34	*Magnolia grandiflora*	Magnolia	Seeds	Magnoliaceae
35	*Melia azedarach*	Indian lilac	Stem or rhizome bark	Meliaceae
36	*Michelia champaca*	Joy perfume tree	Seed and flower extracts	Magnoliaceae
37	*Mundulea sericea*	Cork bush	Bark	Fabaceae
38	*Muntingia calabura*	Strawberry tree	Roots, leaves and fruits	Muntingiaceae
39	*Myrtus communis*	Myrtle	Leaves	Myrtaceae
40	*Nerium oleander*	Oleander	Flowers, leaves	Apocynaceae
41	*Parkia biglandulosa*	Badminton ball tree	Leaves	Fabaceae
42	*Parkia javanica*	Tree bean	Sprout, stem, bark and leaves	Fabaceae
43	*Phyllanthus acidus*	Star gooseberry	Leaves	Phyllanthaceae
44	*Pimenta dioica*	Jamaica pepper	Whole plant	Myrtaceae
45	*Pinus roxburghii*	Chir pine	Cone, needle and bark	Pinaceae
46	*Platanus orientalis*	Chinar	Stem bark	Platanaceae
47	*Plumeria rubra*	Frangipani	Flowers, leaves	Apocynaceae
48	*Prosopis cineraria*	Khejri or Loong tree	Leaves	Fabaceae
49	*Pterospermum acerifolium*	Maple-leaved bayur tree	Leaves	Malvaceae
50	*Salix caprea*	Goat willow	Bark, flowers	Salicaceae
51	*Santalum album*	Sandalwood	Heartwood	Santalaceae
52	*Saraca asoca*	Ashoka tree	Flower	Fabaceae
53	*Schinus terebinthifolius*	Brazilian pepper-tree	Bark	Anacardiaceae
54	*Schleichera oleosa*	Ceylon oak	Bark, leaves and roots	Sapindaceae

55	*Sesbania grandiflora*	August flower, gaach-munga	Roots, bark, gum	Fabaceae
56	*Sesbania sesban*	Common sesban, Jayanti	Seed	Fabaceae
57	*Sterculia foetida*	Poon tree, Jungli badam	Seed	Malvaceae
58	*Suregada multiflora*	False Lime	Leaves	Euphorbiaceae
59	*Swietenia mahagoni*	West Indian mahogany	Seeds	Meliaceae
60	*Symplocos racemosa*	Lodh tree	Bark	Symplocaceae
61	*Tabebuia rosea*	Pink trumpet tree	Leaves	Bignoniaceae
62	*Tabernaemontana divaricata*	Crape jasmine	Stem, bark and leaves	Apocynaceae
63	*Tamarix dioica*	Salt-cedar	Aerial part	Tamaricaceae
64	*Tecomella undulata*	Marwar teak	Bark	Bignoniaceae
65	*Terminalia arjuna*	White Marudah	Bark, stem and leaves	Combretaceae
66	*Thespesia populnea*	Indian tulip tree, Paras pipal	Bark	Malvaceae
67	*Toona ciliata*	Red cedar	Fruit, bark, and roots	Meliaceae
68	*Trewia nudiflora*	False white teak	Seed	Euphorbiaceae
69	*Vitex trifolia*	Indian three-leaf vitex	Leaves	Lamiaceae
70	*Wrightia arborea*	Woolly dyeing rosebay	Leaves	Apocynaceae
71	*Xanthium strumarium*	Cocklebur	Roots	Asteraceae

Additionally, many more traditionally-used medicinal plants have been in focus for anticancer activity. Some examples are *Kedrostis foetidissima* (Pavithra and Saravanan, 2020), *Cissus trifoliata* (Méndez-López et al., 2020), *Saposhnikovia divaricata* (Urbagarova et al., 2020), *Carpesium abrotanoides* (Chai et al., 2019), *Anethum graveolens* (Al-Sheddi et al., 2019), *Paeonia lactiflora* (Xiang et al., 2019), *Acridocarpus orientalis* (Balhamar et al., 2019), *Crateva adansonii* (Zingue et al., 2020), *Kaempferia rotunda* (Islam et al., 2019), *Prunus mume* (Bailly, 2020), *Rhus trilobata* (Varela-Rodríguez et al., 2019), *Reynoutria japonica* (Zhang et al., 2019), *Gleditsia sinensis* (Cai et al., 2019), *Securidaca longipedunculata* (Ngulde et al., 2019), etc.

CONCLUSION

Plants are the prime source of highly effective drugs for the treatment of various types of cancers (Pan L et al., 2012). Sometimes the actual compounds obtained from plants may not serve as drugs but they provide leads for the development of potential novel drug candidates. Recently, omics approaches have been successfully employed to work out biosynthetic pathways of many anticancer phytomolecules and attempt their heterologous expression. For example, the biosynthetic pathway to cyclopamine, a steroid alkaloid obtained from *Veratrum californicum* (Melanthiaceae) that shows promising antineoplastic activities (IPI-926, a semi-synthetic analog of cyclopamine has shown promise against several cancers including pancreatic cancer and leukemia and has been under clinical trials), has been worked out up to pathway intermediate verazine (Augustin et al., 2015), which has also been successfully produced in the seeds of oilseed crop *Camelina sativa* (Brassicaceae) (Augustin et al., 2017). With the emergence of new technologies, some of the agents, which failed earlier in the clinical studies, are now receiving renewed interest. Several new proteins have been identified, which play significant regulatory effects on tumor cell cycle progression. Molecules obtained from plants are the source of inhibitors for the action of these key proteins. These molecules have the potential for development into anticancer drugs. Currently, there is active interest in utilizing new chemopreventive green products from renewable plant sources. In future, the traditional-modern synergistic approach could effectively increase the pace of new drug discovery.

ACKNOWLEDGEMENTS

The authors are grateful to the Council of Scientific and Industrial Research (CSIR), India, for its continued support at various stages for projects and facilities in their work. Authors also thank Dr. Ashutosh K. Shukla, Principal Scientist, CSIR-CIMAP, Lucknow, for critical reading of the manuscript.

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