Annals of Phytomedicine 4(1): 37-45, 2015

Journal homepage: www.ukaazpublications.com

ANNALS OF PHYTOMEDICINE
An International Journal

ISSN : 2393-9885

Review

Herbal medicinal plants as an anticancer agents

Picheswararao Polu, Udupa Nayanabhirama* and Saleemulla Khan

Department of Pharmacognosy, Manipal College of Pharmaceutical Sciences, Manipal, Karnataka-576104, India

**Professor and Research Director (Health Sciences), Manipal Univesity, Manipal, Karnataka-576104, India*

Received March 20, 2015: Revised April 4, 2015: Accepted April 20, 2015: Published online June 30, 2015

Abstract

Cancer is known to be the second most common cause of death, surpassed only by cardiovascular disease. So there has been intense research on various plant resources to develop novel anticancer agents. From the past several years, medicinal plants have been proved to be an important natural source for cancer therapy with fewer side effects. There are many natural cytotoxic drugs available, which needs further improvement and development of new drugs. The basic aim of this review is to explore the potential of newly discovered anticancer compounds from medicinal plants, as a lead for anticancer drug development. It will be helpful to explore the medicinal value of plants and for new drug discovery from them for the researchers and scientists around the globe.

Key words: Anticancer agents, medicinal plants, cancer prevention, apoptosis, cytotoxicity

1. Introduction

Cancer is known to be the second most common cause of death, surpassed only by cardiovascular disease. Based on the ACS report 2014, nearly 1 in every 4 deaths can be attributed to cancer with a possibility of 585,720 deaths due to cancer this year in USA. In 2012, there were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) reported by IARC worldwide. Breast and ovarian cancers are the major cause of cancer death in American women. Studies revealed that in India, 555,000 national cancer deaths in 2010. About 42% of male and 18% of female cancer deaths are due to tobacco-related products. Despite tremendous advances in the cancer chemotherapy, search for new and better agents is continued. Compounds of natural origin have provided new and potential leads for cancer chemotherapy in the past; many of them are drug of choice in cancer treatment. For instance, taxol for breast cancer, vinca alkaloids for leukemia, podophyllum, etoposides and capototheca, *etc.* are some of the natural products in clinical use. Herbs these days are also being used as chemoprotectant against cytotoxicity caused by anticancer drugs. So the present review is aimed to explore the potential anticancer compounds from the medicinal plants.

2. Medicinal plants with anticancer activity

The list of the plants having anticancer activity and the chemical constituents responsible for its activity are given in Table 1. A brief discussion about each plant was given below.

Author for correspondence: Professor Udupa Nayanabhirama
Professor and Research Director (Health Sciences), Manipal Univesity, Manipal, Karnataka-576104, India
E-mail: n.udupa@manipal.edu
Tel.: +91-9845547746

***Allium sativum* Linn.:** Commonly known as garlic, which contains chemical constituents like allicin, alliin, sallyl-cysteine and diallylsulphide, *etc.* Pharmacological properties of allium is due to the presence of allicin which is a precursor for several compounds containing sulphur (Charfenberg *et al*., 1990). Due to the presence of alliin in garlic oil, it inhibits prostaglandin dependent cancers. Metastasis in lung cancer was prevented by diallyl trisulphide present in it (Belman, 1983). Studies shown that the extract of garlic exhibited cytotoxicity against bladder, stomach, lung and breast cancer cell lines by MTT assay (Milner, 1996).

***Actinidia chinensis* Planch.:** Commonly known as kiwi fruit, its immunomodulatory and anticancer activities are due to the presence of polysaccharide known as ACPS-R.

***Aloe vera* Tourn. ex Linn.:** It contains aloe-emodin which inhibits the metastasis and activates the macrophages for anticancer activity (Pecere *et al*., 2000). Its immunostimulant activity against cancer cells is due to the presence of chemical known as acemannan (Wasserman *et al*., 2002).

***Ananas comosus* (Linn.) Merrill.:** In the treatment of leukemias bromealin (mixture of protease + other enzymes) is used, which inhibits the growth of the cancer by enhancing the cytotoxic activity of macrophages and monocytes.

***Angelica sinensis* Linn.:** Used to treat cervical cancer. AR-4, a polysaccharide of the plant responsible for its immunomodulatory activities which includes stimulation of immunce cell proliferation, interferon production, *etc*.

***Annona species* Linn.:** Acetogenins from the plant is effective in treatment of nasopharyngeal carcinoma and it shows cytotoxicity against sarcoma and leukemia.

***Astragalus membranaceus* Bunge:** Used to treat advanced stage of liver cancer due to the presence of swainsonine, a derivative of the plant. Studies shown that, using the plant with the combination of ginseng, shown a highest survival rate in liver cancer patients (Wang and Shimura, 1991).

***Betula utilis* D. Don:** Commonly known as birch, found to be effective in treatment of prostate cancer. Betulin is an active constituent, which can easily convert into betulinic acid responsible for its cytotoxic activity against liver and lung cancer cell lines.

***Camellia sinensis* (Linn.) O.Kuntze:** Commonly known as green tea. It is a potential antioxidant because of the polyphenols present in it. It fights against cancer by removing free radicals from the body. Epigalloacatechin gallate (EGCG), a polyphenol in green tea decrease the number of leukemia cells in the patients with a form of blood cancer known as chronic lymphocytic leukemia (CLL). Daily consumption of green tea (5g/day) protects the body against stomach, colon and lung, *etc*. cancers (Lea *et al*., 1993).

***Catharanthus roseus* G. Don:** Commonly known as Madagascar periwinkle, anticancer activity of the plant is due to the presence of major alkaloids known as vincristine and vinblastine. Vinblastine shows the anticancer activity by inhibiting the microtubule formation in cancer cells and its adverse effects includes loss of hair, bone pain and dizziness, *etc*. (Jean Bruneton, 1993). Vincristine sulphate inhibits the process of mitosis in cancer cells, and it is useful in treatment of acute leukemia in children and lymphocytic leukemia. It is also useful in treatment of Hodgkin disease, Wilkins tumor and reticular cell sarcoma (Nobel, 1990).

***Colchicum luteum* Baker:** Colchicine, a tropolone alkaloid responsible for its anticancer activity by showing antimitoitic activity and used for dispersion of tumors and other neoplastic diseases (Jean Bruneton, 1993).

***Combretum caffrum* (Eckl. & Zeyh) Kuntze:** Combretastatin, constituent of the plant responsible for its activity against cancer by inhibiting the blood supply to the tumor cells.

***Curcuma longa* Linn:** Curcumin is the main constituent responsible for its anticancer activity by inhibiting the PGE-2 (Nagabhushan and Bhide, 1992). The protective effects against cancer are due its direct antioxidant activity. Its antitumor activity is due to involvement in various pathways of cancer like NF-κB, AP-1 and transcriptional factor, *etc*. (Plengsuriyakarn *et al*., 2012). It arrests the cancer cells proliferation in G_2/S phase and induces apoptosis. It is also useful in the treatment of breast, stomach, skin, prostate and lung cancers (Kikuzaki and Nakatani, 1993).

***Echinacea angustifolia*:** By activating the macrophages arabinogalacton protects body from cancer. It is used in treatment of oseophagus and colon cancers (Jean Bruneton, 1993).

***Fagopyrum esculentum* Moench:** Amygdalin, a natural cyanogentic glycoside which contains benzaldehyde and cyanidine responsible for its anticancer activity. β-glucosidase a liver enzyme which breaks molecule into glucuronic acid. Glucuronidase, an enzyme present in higher concentrations in cancer cells, which helps to break glucuronic acid into cyanide which kills cancer cells (Jean Bruneton, 1993).

***Ginkgo biloba* Linn.:** By regulating the platelet activating factor, it inhibits the cancer growth (Tyler, 1994). Studies shown that it helps in protecting the DNA from nuclear radiations (Kleijnen and Knipschild, 1992).

***Glycine max* Merrill:** Isoflavones such as genistein, daidzein and saponins isolated from the plant responsible for its activity. Genistein works by blocking angiogenesis, act as atyrosine kinase inhibitor and inducing apoptosis. It helps in inhibiting the growth and spreading of various cancers such as uterus, breast, cervical, ovarian, testis, prostate and lung, *etc*.

***Glycyrrhiza glabra* Linn.:** Licochalcone-A, compound isolated from the plant shows anticancer activity by inhibiting the growth and spreading of the cancer cells, specifically in prostate cancer by inhibiting the apoptosis and mitosis of cancer cells. Glycyyrhizin, a glycoside of the plant helps in inhibition of spreading and growing of lung cancer and fibrosarcomas (Ambasta, 2000).

***Gossypium barbadense* Linn.:** Gossypol, a constituent from the plant acts as an anticancer agent by inducing the apoptosis and arresting cell cycle at G_0/G_1 phase and it is useful in treatment of different cancers such as pancreas, adrenal gland, prostate, urinary bladder, breast, colon, liver, brain tumors and leukemias, *etc*. The negative isomer of gossypol, *i.e*. (–) gossypol which helps in inhibition of growth and spreading of radiotheraphy resistant cancers of breast, lung, head and neck and brain by inducing the apoptosis (Ambasta, 2000).

***Lentinus edodes* (Berk.) Pegler:** Lentinan, a β-glucan present in the mushroom showed cytotoxicity against lung cancer cell line by MTT assay (Mizuno, 1995) and it acts by increasing the production of natural killer cells and macrophages, which kills the cancerous cells (Mizuno *et al*., 1995). Other edible mushrooms belonging to the family shown anticancer activity, hypolipidemic activity and antithrombotic activity due to the presence of various steroids, terpenes and polysaccharides.

***Linum usitatissimum* Linn.:** Commonly known as flax seed, which contains high amount of lignans. Breast cancer activity of the plant is due to conversion of lignans into enterolactone and enterodiol (mammalian lignans) by bacterial fermentation in colon (Thompson *et al*., 1991) which has structural similarity with estrogens and can bind to oestrogen receptors, thereby inhibits the growth of breast cancer cells (Serraino *et al*., 1991, 1992).

***Mentha species* Linn.:** Essential oils of the plant species contains phenolic compounds which acts as a powerful antioxidants, by fighting against free radicals it acts as an anticancer agent (Attele *et al*., 1999). Monoterpene ketones present in *Mentha piperta* oil causes inhibition of carcinogen by acting directly on metabolites (Yun, 1996; Yun and Choi, 1990).

***Ochrosia elliptica* Labill.:** Ellipticine and 9-methoxy ellipticine, monomeric alkaloids of the plants having potential cytotoxic activity by binding to DNA is of cancer cells (Yun and Choi, 1995). Reports have shown that this plant used in treatment of breast and kidney cancers.

***Panax ginseng* Mey.:** Commonly known as ginseng, lowers the cancer risk in humans (Jeena *et al*., 1999). Its main constituents are a group of 6 triterpenoid saponins known as ginsenosides (Cragg *et al*., 1993). Its activity is due to induction of cell death by either necrosis or apoptosis (Yue *et al*., 2007). Its cytotoxic studies were done on various cancer cell lines which include larynx, pancreas, stomach, bladder and breast, *etc*. (Ali, 1997).

***Picrorrhiza kurroa* Hook.f.:** Commonly known as kutki and its active constituents are picrosides-I, II and III and kutkoside. It shows activity against liver by acting as powerful antioxidant in liver.

***Podophyllum* Linn.:** Podophyllin is the active constituent of the plant species, whose activity is similar to that of vinca alkaloids. It is used in treatment of Hodgkin's disease, non-Hodgkin's lymohoma, leukemia, bronchogenic carcinoma, ovarian and testicular cancers.

***Taxus species* Linn.:** Commonly known as pacific yew and species includes *Taxus brevifolia, Taxus yunnanensis, Taxus baccata* and *Taxus wallichiana*. All the plant species contain taxanes which include paclitaxel and docetaxel are the constituents responsible for its activity. Its activity is different from that of vinka alkaloids and podophyllin. By crosslinking the microtubules, it stops the division of the cancer cells. It is used in treatment of leukemia's, breast, ovarian, lung and colon cancers.

***Tinospora cordifolia* (Willd.) Miers ex Hook.f. & Thoms.:** Recent studies reported that, ethanolic extract of the plant causes significant cytotoxicity and apoptosis effects on human breast cancer cell lines, *i.e*. MCF-7 and MDA MB 231 (Maliyakkal *et al*., 2013). Palmitine, an alkaloid from the plant shown anticancer activity against DMBA induced carcinogenesis in Swiss albino mice model (Huma Ali and Savita, 2013). Sesquiterpenoid and diterpenoid lactones from the plant shown cytotoxicity against throat, cervix and lung cancer cell lines.

***Withania somnifera* Dunal:** Recent studies showed that ethanolic extract of the plant causes cell cycle arrest at G_2/M phase in human breast cancer cell lines (Maliyakkal *et al*., 2013). Withanolide D and withaferin A are compounds from the plant, inhibit the growth and spreading of the cancerous cells. Cytotoxic potential of the plant is due to its free radical scavenging activity (Devi, 1996). When compared with doxorubicin, withanolides of the plant showed significant inhibition in the growth of lung, breast and colon cancer cell lines (Devi *et al*., 1996).

***Zingiber officinale* Rosc.:** Cytotoxic activity of the plant is due the presence of pungent vallinoids like 6-gingerol, shagols, gingerone and 6-paradol. 6-shagol from the plant showed anticancer activity by inducing apoptosis and by inhibiting the formation of new blood vessels, particularly in patients with ovarian cancer (Kikuzaki and Nakatani, 1993).

3. Plant derivatives with anticancer activity

The list of the plant derivatives having anticancer activity and the particular constituents responsible for its activity are given in Table 2. A brief discussion about each derivative was also given in this table.

Berbamine: A bisbenzylisoquinoline alkaloid from Berbamine. It was found that it inhibits the tyrosine kinase and induces apoptosis in chronic myeloid leukemia (Xie *et al*., 2009). Recent studies proved that it acts by inducing caspase-3- dependent apoptosis of NB4 cells (leukemic cancer) (Xu *et al*., 2006).

Berberine: An isoquinoline alkaloid obtained from Berberis species, *Tinospora cordifolia, Hydrastis canadensis, etc*. Recent studies showed its *in vitro* and *in vivo* anticancer activity in prostate, breast, lung, liver and osteosarcoma cancer cell lines (Wang *et al*., 2011; Patil *et al*., 2010).

Betulinic acid: Is a pentacyclic triterpenoid from *Betula alba*. It acts by triggering the mitochondrial pathway in apoptosis, thereby causes the cell death (Fluda, 2008).

Bruceatin: Studies have shown that its activity against HeLa cell lines and rabbit reticulocytes by irreversible inhibition of protein and DNA synthesis (Liaoo *et al*., 1976).

β-lapachone: Is a water insoluble naphthaquinone obtained from *Tabebuia avellanedae* (Li *et al*., 2000). By inhibiting topoisomerase I and II, it showed its anticancer activity in pancreatic, lung and breast cancer cell lines. Because of its poor solubility and systemic toxicity, the compound converted into gold nanoparticles for cancer therapy (Jeong *et al*., 2009).

Camptothecin: An alkaloid from *Camptotheca acuminate*, because of its poor solubility and toxicity new chemical moieties like itinotecan, topotecan, 9-amino camptothecin and rubitecan, *etc.* were chemically synthesized. Cytotoxicity of these compounds is due to inhibition of topoisomerase I (Srivatsava *et al*., 2005). As a second line treatment, topotecans were used in ovarian and lung cancer patients (Creemers *et al*., 1996). Irinotecan was used for colon cancer as a first and second line treatment (Fuchs *et al*., 2006).

Colchicine: An alkaloid from *Colchicum autumnale* and *Gloriosa superba*. It acts by arresting the cell cycle at mitosis. 3-demethyl colchicine, colchicoside, thiocolchicocide are the derivatives of colchicine synthesized chemically because of its toxic nature (Dubey *et al*., 2008).

Combretastatin A-4: A naturally occurring stilbene from *Combretum caffrum*. It acts by disrupting the tubulin and thereby changing the morphology of endothelial cells. It is developed into a nano formulation (2^{nd} phase of clinical trials) because of its poor solubility (Thomso *et al*., 2006; Ley *et al*., 2007).

Cucurbitacin: A tetracyclic triterpenoid from cucurbitaceae species. Their anticancer activity is due to inhibition of JAK 2 activity and transcriptor 3 activator (STAT3) in breast, prostate and nasopharynx cancer cell lines (Molavi *et al*., 2008). Because of its water insoluble nature and non-specific toxicity, its polymeric form is used to deliver the compound (Bermard and Olayinka, 2010).

Curcumin: Is a polyphenolic compound from turmeric. Its activity is by inducing apoptosis and modulation of cell cycle. But the exact mechanism of action of the compound is still not clear. 1^{st} and 2^{nd} clinical phase trails are going on the compound for colorectal cancer (Sa *et al*., 2010). Studies showed that the compound in higher doses was safe and it was reported in 1^{st} phase of clinical trials (Goel *et al*., 2008).

Daphnoretin: Is a coumarin derivative showing potent anticancer activity (Lu *et al*., 2011). It shows cytotoxicity in human hepatoma Hep 3B cell lines by inhibiting hepatitis B surface antigen expression (Diogo *et al*., 2009).

Diadzein and Genistein: Are the aglycon moieties, found in isoflavones of soya and its activity is due to inhibition of 3A4-mediated metabolism (Moon *et al*., 2006). Genistein used in breast and ovarian cancer due to inhibition of cell proliferation. These compounds are also capable of chemically induced lung, prostate, bladder and blood cancers (Dixon and Ferreira, 2002).

Ellipticine: An alkaloid from Apocyanaceae family and its activity is due to inhibition of topoisomerase II and intercalation of DNA. Reports shown that it inhibits growth and induces apoptosis in hepato carcinoma cells ($HepG_2$) (Kuo *et al*., 2006).

Emodin: It is an anthraquinone compound and it induces apoptosis in liver, lung, ovarian and blood cancer cell lines by different pathways (Huang *et al*., 2009).

Flavopiridol: Is a semisynthetic derivative from plant alkaloid rohitukine. Its anticancer activity is due to the inhibition of cell cycle at G_1 or G_2 phase by interferring with cyclic dependent kinase. Presently, it is under 1st phase of clinical trials for treating solid tumors and 2nd phase of clinical trials for treating renal cellular carcinoma and colorectal carcinoma (Mans *et al*., 2000).

Harringtonine and Homoharringtonine: Are the esters of cephalotaxine alkaloid. By inhibiting the protein synthesis and chain elongation homoharringtone acts as an anticancer agent. Both these compounds are effective against acute and chronic myeloid leukemias (Cragg and Newman, 2005; Efferth *et al*., 2007).

Indirubin and Meisoindigo: Its anticancer activity is due to inhibition of cyclin dependent kinase, which arrest the cell cycle and it also inhibit the proliferation of cancer cells. Clinically, it is effective against chronic myeloid leukemia (Nam *et al*., 2005; Liu *et al*., 1996). Because of its poor solubility and absorption, its derivative meisoindigo has been synthesized chemically.

Ingenol 3-o-angelate: Is a diterpene ester and derivative of ingenol obtained from *Euphorbia peplus*. By activating the PKC, it causes necrosis of the cancerous cells. Presently, it is under 2nd phase of clinical trials for the treatment of actinic keratosis and basal cell carcinoma (Hampson *et al*., 2005).

4-Ipomeanol: Is a furan derivative from *Ipomea batatus*. It acts by cytochrome p-450 mediated conversion into DNA-binding metabolite. It showed good cytotoxic potential against lung cancer in pre-clinical stages but unfortunately it showed poor results in human trails (Ancuceanu and Istudor, 2004).

Irisquinone: Is a benzoquinone derivative showed good anti-neoplastic potential against rodent tumors and acts as a chemosensitizer (Hazra *et al*., 2004).

Phenoxodiol and Protopanaxadiol: Is a synthetic analogue of naturally occurring gensistein. It acts by inducing apoptosis by inhibiting the membrane electron transport and cell proliferation. Presently, it is under 3rd phase of clinical trials for ovarian cancer and initial stage of clinical trials for cervical and prostate cancer (Herst *et al*., 2009). Protopanaxadiol is a triterpenoid analogue from ginseng saponins. It acts by inducing apoptosis and shows cytotoxicity against lung, breast and colorectal cancer cell lines. Presently, it is under 1st phase of clinical trials for treatement of lung cancer (Pan *et al*., 2010).

Phodophyllotoxin: Etoposide and teniposide are the semisynthetic analogues of phophyllotoxin, proved to be potential anti-neoplastic agents against lymphomas, bronchial and testicular cancers (Shoeb, 2006).

Salvicine: Is a diterpenoid quinone from *Salvia prionitis*. Reports shown that it is a good anticancer activity in both *in vitro* and *in vivo* against malignant tumors by inhibiting topoisomerase II (Deng *et al*., 2011).

Silvestrol: Was found to be effective against prostate and breast cancer. It revealed that mitochondrial pathway which triggers the extrinsic pathway of apoptosis of human prostate cancer cell lines (LNCaP). Episilvestrol is an epimer of silvestrol, proved to be less cytotoxic than silvestrol (Kinghorn *et al*., 2009; Kim *et al*., 2007).

Taxanes: They act by binding to microtubles and stops the mitosis of the cancerous cells (Hait *et al*., 2007). Paclitaxel and its semi-synthetic derivative docotaxel are important derivatives of taxanes and they are the choice of drugs as 1st and 2nd line treatment for lung, ovarian and prostate cancers (Kingston, 2007).

Vinca alkaloids: They act by inhibiting the cell proliferation by binding to tubulin during mitosis which leads to apopotosis of cancerous cells. Vincristine and vinblastine are the natural compounds; vinorelbine and vindensine are semisynthetic analogues of vinka alkaloids and presently they are in phase II clinical trials. In combination with chemotherapeutic agents, these compounds are effective against advanced testicular cancer, lymphomas, leukemia's and breast cancers (Cragg *et al*., 2005). Vinorelbine and vinflurine are the other two synthetic analogues which showed reduced cytotoxicity in animal models (Okouneva *et al*., 2003; Simeons *et al*., 2008).

4. Conclusion

From the preceding review, it can be concluded that herbal medicinal plants and its derivatives are active against different type of cancers like lymphomas, breast, ovarian, lung, liver, stomach, prostate and testicular cancers. Hence, there is hope in the pharmaceutical industry, that even more powerful commercial drugs can be developed sooner, using plant derivatives, to effectively treat cancer and save mankind.

Acknowledgements

The authors thank Manipal University, Manipal College of Pharmaceutical Sciences, Manipal, India for providing the facilities to carry out this study.

Conflict of interest

We declare that we have no conflict of interest.

Table 1: Herbal medicinal plants with anticancer activity

S.No.	Botanical name	Family	Common name	Active constituent
1.	*Allium sativum*	Lilliaceae	Garlic	Alliin, allicin, alliinase, S-allyl-cysteine (SAC), diallyl sulphide (DADS)
2.	*Actinidia chinensis*	Actinidiaceae	Kiwi fruit, china gooseberry	Polysaccharide known as ACPS-R
3.	*Aloe ferax, Aloe barbadensis*	Lilliaceae	*Aloe vera*	Aloe-emodin, emodin, aloin
4.	*Ananas comosus*	Bromeliaceae	Pine apple	Bromelain
5.	*Angelica sinensis*	Umbelliferae	Angelica	Polysaccharide fraction known as AR-4
6.	*Annona species*	Annonaceae	Monkey species	Acetogenins
7.	*Arctium lappa*	Compositae	Burdock	Potential anticancer factors
8.	*Astragalus membranaceus*	Papillonaceae	—	Swainsonine
9.	*Betula utilis*	Betulaceae	Bhojpatra	Betulin
10.	*Camellia sinensis*	Theaceae	Tea plant	Epigallocatechin gallate
11.	*Catharantus roseus*	Apocynaceae	Vinca	Vincristine and vinblastine
12.	*Chlorella pyrenoidosa*	Oosystaceae	—	Lysine
13.	*Colchicum luteum*	Lilliaceae	Colchicum	Colchicum democlocine
14.	*Combretum cuffrum*	Combrittaceae	—	Combretastatin
15.	*Curcuma longa*	Zinziberaceae	Turmeric	Turmerone, curcumine
16.	*Echinacea angustifolia*	Asteraceae	Black sampson	Arabinogalactan
17.	*Fagopyrum esculentum*	Polygoneaceae	Vitamin P	Amygdalin, rutin
18.	*Ginkgo biloba*	Ginkoaceae	Kew tree	Ginkgolide – B, A, C and J
19.	*Glycine max*	Leguminosae	Soybean	Isoflavones, protease inhibitors, saponins and phytosterols
20.	*Glycyyrhiza glabra*	Leguminosae	Liquorice	Glycyrrhizin
21.	*Gossypium barbadense*	Malvaceae	Raw cotton	Gossypol
22.	*Gyrophora esculenta*	Umbellicariaceae	Mushroom	Polysaccharide β-glucans, α-glucans and galactomannans
23.	*Lentinus edodes*	Agaricaceae	—	Lentinan
24.	*Linum usitatissimam*	Linaceae	Flax seeds, linseed	Cynogentic glycosides, lignans
25.	*Mentha species*	Labiateae	Pudina	Monoterpene ketones
26.	*Ochrosia elliptica*	Apocynaceae	—	Ellipticine and 9-methoxy ellipticine are pyrindocarbazole alkaloids
27.	*Panax ginseng*	Aralaceae	Ginseng	Ginsenosides, panaxosides
28.	*Picrorrhiza kurroa*	Scrophulariaceae	Picrorrhiza (kutki)	Picrosides I, II, III and kutkoside
29.	*Podophyllum hexandrum*	Podophyllaceae	Podophyllum	Podophyllin, astragalin
30.	*Taxus brevifolia*	Taxaceae	Pacific yew	Taxanes, taxol cepholomannine
31.	*Tinospora cordifolia*	Menispermaceae	Guduchi	Berberine, palmitine, tinosporside
32.	*Withania somnifera*	Solanaceae	Ashwagandha	Withanolides, withaferin
33.	*Zingiber officinale*	Zingiberaceae	Ginger	Ginge rols, shagols, zingerone

Table 2: Plant derivatives as anticancer agents

S.No	Semisynthetic analogs of plant derivatives	Species and genus name	Experiments on various cancer cells	Mechanism of action	Reference
1.	Vindesine and vinorelbine	*Catharanthus roseus*	Leukemia's, lymphomas, lung cancer, breast and advanced testicular cancer	Mitotic block	Cragg and Newman, 2005
2.	Vinflunine	*Catharanthus roseus*	Reduced toxicity in animal models	Mitotic block	Okouneva *et al*., 2003; Simeons *et al*., 2008
3.	Etoposide and Teniposide	*Podophyllum emodi and Podophyllum pletatum*	Lymphomas, bronchial and testicular cancers	-	Shoeb, 2006
4.	Taxol	*Taxus brevifolia, Taxus bacata*	Metastatic, breast, ovarian, lung, prostate cancer and lymphoid malignancies	Antimitotic	Kingston, 2007
5.	Taxotere	*Taxus brevifolia, Taxus baccata*	Used in patients resistant to placlitaxel	Antimitotic	Hait *et al*., 2007
6.	Topotecan	*Camptotheca acuminate*	Epithelial ovarian cancer and small cell lung cancer	DNA topoisomerase I inhibition	Creemers *et al*., 1996
7.	Irinotecan	*Camptotheca acuminate*	Metastatic and colorectal cancer	DNA topoisomerase I inhibition	Fuchs *et al*., 2006
8.	Exatecan	*Camptotheca acuminate*	Potential antitumor activity both *in vitro* and *in vivo*	DNA topoisomerase I inhibition	Mineko *et al*., 2000
9.	LE-SN-38	*Camptotheca acuminate*	Various cancer cell lines	DNA topoisomerase I inhibition	Zhang *et al*., 2004
10.	Berbamine	*Berberis amarensis*	Chronic myeloid leukemia	Caspase - 3 - dependent apoptosis	Xie *et al*., 2009; Xu *et al*., 2006
11.	Berberine	*Hydrastis canadensis* L., *Berberineeris sp & Arcungelisia flaw*	Osteosarcoma, lung, liver prostate and breast cancer	Not known	Patil *et al*., 2010
12.	Beta-lapachone	*Tabebuia Avellanedae*	Breast cancer, prostate cancer, lung cancer, pancreatic cancer and promyelocytic leukemia	Inhibition of topoisomerase I and II	Li *et al*., 2000;
13.	Betulinic acid	*Betula alba*	Exhibits anticancer activity in humans	Triggers mitochondrial pathway of apoptosis	Fluda, 2008
14.	Colchicine	*Colchicum autumnale and Gloriosa superba* L.	Leukemia and solid tumors	Antimitotic	Dubey *et al*., 2008
15.	Combretastatin A-4	*Combretum caffrum* Kuntze	Phase II clinical trials	Tubulin structure disruption	Thomso *et al*., 2006 Ley *et al*., 2007
16.	Cucurbitachin	*Cucurbitaceae* species	Various cancer cell lines	Inhibits signal transducer / JAK 2 activity and activates STAT3 pathway	Molavi *et al*., 2008; Bernard and Olayinka *et al*., 2010

17.	Curcumin	*Curcuma longa*	Colorectal cancer, multiple myeloma and pancreatic cancer	Exact mechanism of action is still unknown	Goel *et al*., 2008
18.	Daphnoretin	*Wikstroemia indica*	Ehrlich ascites carcinoma, Human hepatoma Hep3B cells	Suppression of protein and DNA synthesis	Diogo *et al*., 2009
19.	Diadzein and Genistein	*Lupinus* species, *Vicia faba, Glycine max, Psoralea corylifolia*	Ovarian, breast cancer and chemically induced cancers of stomach, bladder and lung	Inhibits 3A 4 - mediated metabolism and oxidative metabolism	Dixon and Ferreira *et al*., 2002
20.	Elipticine	*Ochrosia borbonica, Ochrosia elliptica*	Various cancer cell lines	DNA intercalation and inhibition of topoisomerase II	Kuo *et al*., 2006
21.	Emodin	Rhizome of rubarb	Lung, liver, ovarian and blood cancer	Apoptosis of cancer cells by several pathways	Huang *et al*., 2009
22.	Flavopiridol	*Amoora rohituka and Dysoxylum binectariferum*	Colorectal, non-small cell lung cancer, renal cell carcinoma and solid tumors	Inhibits cell cycle progression at G_1 or G_2 phase	Man's *et al*., 2000
23.	Harringtonine and Homoharringtonine	*Cephalotaxus herrintonia*	Acute and chronic myeloid leukemia	Inhibition of protein synthesis and chain elongation during translation	Cragg and Newman 2005; Efferth *et al*., 2007
24.	Indirubin	Chinese herb, Danggui Lonehui Wan	Chronic myeloid leukemia	Inhibits cyclin-dependent kinase	Nam *et al*., 2005
25.	Ingenol 3-o-angelate	*Euphorbia peplus* L.,	Actinic keratosis and basal cell carcinoma	Causes necrosis of tumor by the activation of PKC	Hampson *et al*., 2005
26.	4-Ipomeanol	*Ipomoeca batatas*	Lung specific cancer in animal models	Cytochrome p-450 mediated conversion into DNA - binding metabolities	Ancuceanu and Istudor, 2004
27.	Irisquinone	*Iridaceaclatca pallasii and Iris kumaoensis*	Good activity in transplatable rodent tumors	Acts as a chemosensitizer	Hazra *et al*., 2004
28.	Phenoxodiol	Plant isoflavone, genistein	Ovarian, prostate and cervical cancer	Inhibit plasma membrane electron transport and cell proliferation	Herst *et al*., 2009
29.	Salvicine	*Salvia prionitis* Hance	Malignant tumors	Inhibition of topoisomerase II	Deng *et al*., 2011
30.	Silvestrol	*Aglaia foveolata* Panell	Prostate, breast and lung cancers	Apoptosome/ mitochondrial pathway was involved in triggering extrinsic pathway of programmed cell death of tumor cells	Kinghom *et al*., 2009; Kim *et al*., 2007

References

Ali, Mand Shuaib (1997). Withanolides from the stem bark of *Withania somnifera*. Phytochemistry, **44**(6):1163-1168.

Ambasta, S.P. (2000). The useful plants of India, Fourth Edition, National Institution of Sci. Communication, Delhi, pp:239.

Ambasta, S.P. (2000). The useful plants of India, Fourth Edition, National Institution of Sci. Communication, Delhi, pp:243.

Ancuceanu, R.V and Istudor, V. (2004). Pharmacologically active natural compounds for lung cancer. Altern. Med. Rev., **9:**402-419.

Asthana, R and Raina, M.K. (1989). Pharmacology of *Withania somnifera*- a review. Ind. Drugs, **26**:1-7.

Attele, A.S.; Wu, J.A and Yuan, C.S. (1999). Ginseng pharmacology: multiple constituents and multiple actions. Biochem. Pharmacol., **58**(11):1685-1693.

Belman, S. (1983). Onion and garlic oils inhibit tumor promotion. Carcinogenesis, **4**:1063-65.

Bernard, S.A. and Olayinka, O.A. (2010). Search for a novel antioxidant, antiinflammatory/ analgesic or antiproliferative drug: cucurbitacins hold the ace. J. Med. Plants Res., **4:**2821-2826.

Charfenberg, K.; Wagner, R. and Wagner, K.G. (1990). The cytotoxic effect of ajoene, a natural product from garlic, investigated with different cell lines. Cancer Letter, **53**(2-3):103-08.

Cragg, G.M. and Newman, D.J. (2005). Plants as a source of anti-cancer agents. J. Ethnopharmacol., **100:**72-79.

Cragg, G.M.; Schepartz, S.A.; Suffness, M. and Grever, M.R. (1993). The taxol supply crisis- New NCI policies for handling the large-scale production of novel natural product anticancer and anti-HIV agents. J. Nat. Prod., **56**:1657-68.

Creemers, G.J.; Bolis, Gore M.; Scarfone, G.; Lacave, A.J.; Guastalla, J.P.; Despax, R.; Favalli, G.; Kreinberg, R. and VanBelle, S. (1996). Topotecan, an active drug in the second-line treatment of epithelial ovarian cancer: results of a large European phase II study. J. Clin. Oncol., **14:**3056-61.

Deng, F.; Lu, J.J.; Liu, H.Y.; Lin, L.P.; Ding, J. and Zhang, J.S. (2011). Synthesis and antitumor activity of novel salvicine analogues. Chin. Chem. Lett., **22:**25-28.

Devi, P.U. (1996). *Withania somnifera* Dunal (Ashwagandha): potential plant source of a promising drug for cancer chemotherapy and radiosensitization. Indian J. Exp. Biol., **34**:927-932.

Devi, P.U.; Akagi, K.; Ostapenko, V.; Tanaka, Y. and Sugahara, T. (1996). Withaferin A: a new radiosensitizer from the Indian medicinal plant *Withania somnifera*. Int. J. Radiat. Biol., **69**(2):193-97.

Diogo, C.V.; Felix, L.; Vilela, S.; Burgeiro, A., Barbosa, I.A.; Carvalho, M.J.M.; Oliveira, P.J. and Peixoto, F.P. (2009). Mitochondrial toxicity of the phyotochemicals daphnetoxin and daphnoretin - relevance for possible anticancer application. Toxicol. *In vitro*, **23:**772-779.

Dixon, R.A. and Ferreira, D. (2002). Molecules of interest: genistein. Phytochemistry, **60:**205-211.

Dubey, K.K.; Ray, A.R. and Behera, B.K. (2008). Production of demethylated colchicine through microbial transformation and scale-up process development. Process Biochem., **43:**251-257.

Efferth, T.; Li, P.C.H.; Konkimalla, V.S.B. and Kaina, B. (2007). From traditional Chinese medicine to rational cancer therapy. Trends Mol. Med., **13:**353-61.

Fuchs, C.; Mitchell, E.P. and Hoff, P.M. (2006). Irinotecan in the treatment of colorectal cancer. Cancer Treat. Rev., **32:**491-503.

Fluda, S. (2008). Betulinic acid for cancer treatment and prevention. Int. J. Mol. Sci., **9:**1096-1107.

Goel, A.; Kunnumakkara, A.B. and Aggarwal, B.B. (2008). Curcumin as ''Curecumin'': from kitchen to clinic. Biochem. Pharmacol., **75:**787-809.

Hait, W.N.; Rubin, E.; Ali, E.; and Goodin, S. (2007). Tubulin targeting agents. Update on Cancer Therapeutics, **2:**1-18.

Hampson, P.; Wang, K. and Lord, J.M. (2005). Treatment of actinic keratoses, acute myeloid leukemia therapy, treatment of basal cell carcinoma, protein kinase C activator. Drugs Fut., **30:**1003.

Hazra, B.; Sarma, M.D.; and Sanyal, U. (2004). Separation methods of quinonoid constituents of plants used in oriental traditional medicines. J. Chromatogr. B., **8(**12**):**259-275.

Herst, P.M.; Davis, J.E.; Neeson, P.; Berridge, M.V. and Ritchie, D.S. (2009). The anticancer drug, phenoxodiol, kills primary myeloid and lymphoid leukemic blasts and rapidly proliferating T cells. Haematologica, **94:**928-934.

Huang, Z.; Chen, G. and Shi, P. (2009). Effects of emodin on the gene expression profilingof human breast carcinoma cells. Cancer Detect. Prev., **32:**286-291.

Huma, Ali and Savita, Dixit (2013). Extraction optimization of *Tinospora cordifolia* and assessment of the anticancer activity of its alkaloid palmatine. The Scientific World Journal, **1**-10.

Jean Bruneton (1993). Pharmacognosy, phytochemisty medicinal plants. Lavoisier Publisher., France, pp:832.

Jean Bruneton (1993). Pharmacognosy, phytochemisty medicinal plants. Lavoisier Publisher., France, pp:771-77.

Jean Bruneton (1993). Pharmacognosy, phytochemisty medicinal plants. Lavoisier Publisher., France, pp:151.

Jean Bruneton (1993). Pharmacognosy, phytochemisty medicinal plants. Lavoisier Publisher., France, pp:281.

Jeena, K.J.; Joy, K.L. and Kuttan, R. (1999). Effect of *Emblica officinalis*, *Phyllanthus amarus* and *Picrorrhizakurroa* on N-nitrosodiethylamine induced hepatocardinogenesis. Cancer Lett., **136**:11-16.

Jeong, S.Y.; Park, S.J.; Yoon, S.M.; Jung, J.; Na Woo, H.; Yi, S.L.; Song, S.Y.; Park, H.J.; Kim, C. and Lee, J.S. (2009). Systemic delivery and preclinical evaluation of Au nanoparticle containing β-lapachone for radiosensitization. J. Control Release, **139:**239-245.

Kikuzaki, H. and Nakatani, N. (1993). Antioxidant effects of some ginger constituents. J. Food. Sci., **58**:1407-10.

Kim, S.; Hwang, B.Y.; Su, B.N.; Chai, H.; Mi, Q.; Kinghorn, A.D.; Wild, R. and Swanson, S.M. (2007). Silvestrol, a potential anticancer rocaglate derivative from *Aglaia foveolata*, induces apoptosis in LNCaP cells through the mitochondrial/apoptosome pathway without activation of executioner caspase-3 or -7. Anticancer Res., **27:**2175-2183.

Kinghorn, D.; de Blanco, E.J.C.; Chai, H.B.; Orjala, J.; Farnsworth, N.R.; Soejarto, D.D.; Oberlies, N.H.; Wani, M.C.; Kroll,D.J. and Pearce, C.J. (2009). Discovery of anticancer agents of diverse natural origin. Pure Appl. Chem., **81:**1051-1063.

Kingston, D.G.I. (2007). The shape of things to come: structural and synthetic studies of taxol and related compounds. Phytochemistry, **68**(14):1844-1854.

Kleijnen, J. and Knipschild, P. (1992). *Gingko biloba* for cerebral insufficiency. Br. J. Clin. Pharmacol., **34**;352-58.

Kuo, Y.C.; Kuo, P.L.; Hsu, Y.L.; Cho, C.Y. and Lin, C.C. (2006). Ellipticine induces apoptosis through p53-dependent pathway in human hepatocellular carcinoma HepG2 cells. Life Sciences, **78:**2550-2557.

Ladanyi, A.; Timar, J. and Lapis, K. (1993). Effect of lentinan on macrophage cytotoxicity against metastatic tumor cells. Cancer Immunol and Immunother, **36**:123-26.

Lampe, J.W.; Martini, M.C.; Kurzer, M.S.; Adlercreutz, H. and Slavin, J.L. (1994). Urinary lignan and isoflavonoid excretion in premenopausal women consuming flaxseed powder. Am. J. Clin. Nutr., **60**:122-28.

Lea, M.A.; Xiao, Q.; Sadhukhan, A.K.; Cottle, S.; Wang, Z.Y. and Yang, C.S. (1993). Inhibitory effects of tea extracts and (-)-epigallocatechin gallate on DNA synthesis and proliferation of hepatoma and erythroleukemia cells. Cancer Lett., **68**:231-6.

Ley, C.D.; Horsmany, M.R. and Kristjansen, P.E.G. (2007). Early effects of combretastatin-A4 disodium phosphate on tumor perfusion and interstitial fluid pressure. Neoplasia, **9:**108-112.

Liaoo, L.L.; Kupchan, S.M. and Horwitz, S.B. (1976). Mode of action of the antitumor compound bruceantin, an inhibitor of protein synthesis. Mol. Pharmacol., **12:**167-176.

Liu, X.M.; Wung, L.G.; Li, H.Y. and Ji, X.J. (1996). Induction of differentiation and downregulation of c-myb gene expression in ML4 human myeloblastic leukemia cells by the clinically effective and leukemia agent meisoindigo. Biochem. Pharmacol., **51:**1545-1551.

Maliyakkal, N.; Udupa, N.; Pai, K.S.R. and Rangarajan, A. (2013). Cytotoxic and apoptotic activities of extracts of *Withania somnifera* and *Tinospora cordifolia* in human breast cancer cells. Int. J. of Applied Res. in Nat. Products, **6**(4):1-10.

Mans, D.R.A.; Da Rocha, A.B. and Schwartsmann, G. (2000). Anti-cancer drug discovery and development in Brazil: targeted plant collection as a rational strategy to acquire candidate anticancer compounds. The Oncologist, **5:**185-198.

Milner, J.A. (1996). Garlic: its anticarcinogenic and antitumorigenic properties. Nutr. Rev., **54**:82-86.

Mizuno, T. (1995). Bioactive biomolecules of mushrooms: food function and medicinal effect of mushroom fungi. Food Rev. Int., **11**:7-21.

Mizuno, T. (1995). Shiitake- *Lentinus edodes*: functional properties for medicinal and food purposes. Food Rev. Int., **11**:111-28.

Mizuno, T.; Saito, H.; Nishitoba, T. and Kawagishi, H. (1995). Antitumor active substances from mushrooms. Food Rev. Int., **11**:23-61.

Molavi, O.; Ma, Z.; Mahmud, A. and Alshamsan, A. (2008). Polymeric micelles for the solubilization and delivery of STAT3 inhibitor cucurbitacins in solid tumors. Int. J. Pharm., **347:**118-127.

Nagabhushan, M. and Bhide, S.V. (1992). Curcumin as an inhibitor of cancer. J. Am. Coll. Nutr., **11**:192-98.

Nam, S.; Buettner, R.; Turkson, J.; Kim, D.; Cheng, J.Q.; Muehlbeyer, S.; Hippe, F.; Vatter, S.; Merz, K.H. and Eisenbrand, G. (2005). Indirubin derivatives inhibit Stat3 signaling and induce apoptosis in human cancer cells. PNAS., **102:**5998-6003.

Noble, R.L. (1990). The discovery of the vinca alkaloids-chemotherapeutic agents against cancer. Biochem. Cell Bio., **68**;1344-1351**.**

Okouneva, T.; Hill, B.T.; Wilson, L. and Jordan, M.A. (2003). The effects of vinflunine, vinorelbine, and vinblastine on centromere dynamics. Mol. Cancer Ther., **2:**427-436.

Pan, L.; Chai, H. and Kinghom, A.D. (2010). The continuing search for antitumor agents from higher plants. Phytochem. Lett., **3:**1-8.

Patil, J.B.; Kim, J. and Jayaprakasha, G.K. (2010). Berberine induces apoptosis in breastcancer cells (MCF-7) through mitochondrial-dependent pathway. Eur. J. Pharmacol., **64**(5):70-78.

Pecere, T.; Gazzola, M.V. and Micignat, C. (2000). Aloe-emodin is a new type of anticancer agent with selective activity against neuro-ectodermal tumors. Cancer Res., **60**:2800-2804.

Serraino, M. and Thompson, L.U. (1991). The effect of flaxseed supplementation on early risk markers for mammary carcinogenesis. Cancer Lett., **60**:135-42.

Serraino, M. and Thompson, L.U. (1992). The effect of flaxseed supplementation on the initiation and promotional stages of mammary tumorigenesis. Nutr. Cancer, **17**:153-59.

Shoeb, M.; Celik, S.; Jaspars, M.; Kumarasamy, Y.; MacManus, S.; Nahar, L.; Kong, T.L.P. and Sarker, S.D. (2006). Isolation, structure elucidation and bioactivity of schischkiniin, a unique indole alkaloid from the seeds of *Centaurea schischkinii*. Tetrahedron, **61:**9001-06.

Simoens, C.; Lardon, F.; Pauwels, B.; De Pooter, C.M.J.; Lambrechts, H.A.J.; Pattyn, G.G.O.; Breillout, F. and Vermorken, J.B. (2008). Comparative study of the radiosensitising and cell cycle effects of vinflunine and vinorelbine, *in vitro*. BMC Cancer, **8:**65.

Srivastava, V.; Negi, A.S.; Kumar, J.K.; Gupta, M.M. and Khanuja, S.P.S. (2005). Plant-based anticancer molecules: a chemical and biological profile of some important leads. Bioorg. Med. Chem., **13:**5892-5908.

Thompson, L.U.; Robb, P.; Serraino, M. and Cheung, F. (1991). Mammalian lignan production from various foods. Nutr. Cancer, **16**:43-52.

Thomso, P.; Naylor, M.A.; Everett, S.A.; Stratford, M.R.L.; Lewis, G.; Hill, S.; Patel, K.B.; Wardman, P. and Davis, P.D. (2006). Synthesis and biological properties of bioreductively targeted nitrothienyl prodrugs of combretastatin A-4. Mol. Cancer. Ther., **5:**2886-2894.

Tyler, V. (1994). Herbs of choice: the therapeutic use of phytomedicinals. Haworth Press, New york, pp:32-33.

Wang, F.; Gao, Y.; Gao, L. and Xing, T. (2011). Study on the electrochemical behavior of the anticancer herbal drug berberine and its analytical application., J. Chin. Chem. Soc.**, 58**:61-68.

Wang, J. and Shimura, K. (1991). Enhancing effect of antitumor polysaccharide from *Astralagus*or *radix hedysarum* on C3 cleavage production of macrophages in mice. Mem. Inst. Oswaldo Cruz.., **86**(20):159-164.

Wasserman, L.; Avigad, S.; Nordenberg, J.; Berry, E. and Fenig, E. (2002). The effect of aloe-emodin on the proliferation of a new merkel carcinoma cell line. The Am. J. of Dermatopathology, **24**(1):17-22.

Xie, J.; Ma, T.; Gu, Y.; Zhang, X.; Qiu, X. and Zhang, L. (2009). Berbamine derivatives: a novel class of compounds for antileukemia activity. Eur. J. Med. Chem., **44:**3293-3298.

Xu, R.; Dong, Q. and Gan, X. (2006). Berbamine: a novel inhibitor of bcr/ablfusion gene with potent anti-leukemiaactivity. Leuk. Res., **30:**17-23.

Yue, P.Y.; Mak, N.K.; Cheng, Y.K.; Leung, K.W.; Ng, T.B.; Fan, D.T.; Yeung, H.W. and Wong, R.N. (2007). Pharmacogenomics and the Yin/Yangactions of ginseng: antitumor, angiomodulating and steroidlike activities of ginsenosides. Chinese Med., **2**:6.

Yun, T.K. and Choi, S.Y. (1990). A case-control study of ginseng intake and cancer. Int. J. Epidemiol., **19**:871-76.

Yun, T.K. and Choi, S.Y. (1995). Preventive effect of ginseng intake against various human cancers: a case control study on 1987 pairs. Cancer Epidemiol Biomarkers Prev., **4**:401-08.

Yun, T.K. (1996). Experimental and epidemiological evidence of the cancer-preventive effects of *Panax ginseng* C.A. Meyer. Nutr. Rev., **54**:71-81.