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ANTI-CANCER AGENTS DERIVED FROM PLANT AND DIETARY SOURCES: A REVIEW

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ABSTRACT: Cancer is a disease of deregulated cellular behavior. Acquisition of oncogenic attributes, loss of tumor suppressive functions, evasion of physiological tissue architecture and interactions with the cellular microenvironment enable malignant cells to escape the mechanisms of normal cellular homeostasis in an organism. Cancer cells are therefore able to sustain unlimited proliferation, to thrive under conditions that preclude normal cell survival, and to spread to distant sites through the process of metastasis. Natural products are important sources of new anticancer drugs, new drug leads and new chemical entities. The plant-based drug discovery resulted mainly in the development of anticancer agents including plants (vincristine, vinblastine, paclitaxel, etoposide, camptothecin, topotecan, and irinotecan). Beside this there are numerous agents identified from fruits and vegetables can use in anticancer therapy. The agents include curcumin (turmeric), resveratrol (red grapes, peanuts and berries), genistein (soybean), diallyl sulfide (allium), S-allyl cysteine (allium), allicin (garlic), lycopene (tomato), capsaicin (red chilli), diosgenin (fenugreek), 6-gingerol (ginger), ellagic acid (pomegranate), ursolic acid (apple, pears, prunes), silymarin (milk thistle), anethol (anise, camphor, and fennel), catechins (green tea), eugenol (cloves), indole-3-carbinol (cruciferous vegetables), Limonene (citrus fruits), beta carotene (carrots), and dietary fiber. In this review active principle derived from natural products are offering an excellent opportunity to evaluate not only new chemical classes of anticancer agents but also novel lead compound and potentially relevant mechanisms of action.

INTRODUCTION: In the most general terms, cancer refers to cells that grow out-of-control and invade other tissues. Cells become cancerous due to the accumulation of defects, or mutations, in their DNA. Certain inherited genetic defects (for example, BRCA1 and BRCA2 mutations) and infections can increase the risk of cancer.

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Environmental factors (for example, air pollution) and poor lifestyle choices such as smoking and heavy alcohol use can also damage DNA and lead to cancer. Most of the time, cells can detect and repair DNA damage. If a cell is severely damaged and cannot repair itself, it undergoes so-called programmed cell death or apoptosis. Cancer occurs when damaged cells grow, divide, and spread abnormally instead of self-destructing as they should.

The International Agency for Research on Cancer showed in research that 184 countries of the world had 14.1 million new cancer cases, 8.2 million cancer deaths, and 32.6 million people living with

cancer (within 5 years of diagnosis) in 2012 worldwide [1]. It is projected that there will be 26 million new cancer cases and 17 million cancer deaths per year by 2030 [2]. The main processes of cancer treatment in humans are surgery, radiation, and drugs (chemotherapeutic agents). Cancer chemotherapeutic agents can often provide temporary relief of symptoms, give the patient more time and rarely cures. In recent years, a lot of research has been conducted to the synthesis of potential anticancer drugs. Many hundreds of chemical compounds of a known class of anticarcinogenic agent have been synthesized but have lots of side effects. A successful anticancer drug should kill or inactivate cancer cells without causing excessive damage to normal cells [3, 4]. Therefore there is a constant necessity for developing new, useful and relatively anticancer drugs [5]. Chemical compounds derived from plants have been used to treat human diseases from the dawn of human civilization. Natural products have caught increasing attention over the past few years for their potential as a novel cancer preventive and therapeutic agents [6, 7].

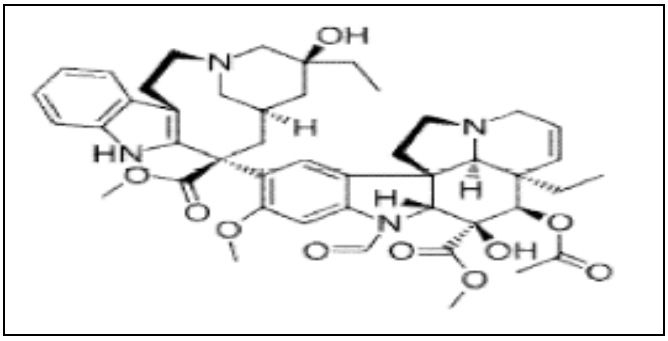
In parallel, there is increasing evidence for the potential ability of plant-derived compounds as inhibitors of various stages of tumor cell formation and associated inflammatory processes, indicating the importance of these products in cancer prevention and therapy.

The search for anti-cancer agents from plant sources started in earnest in the 1950s with the discovery and development of the vinca alkaloids, vinblastine and vincristine, and the isolation of the cytotoxic podophyllotoxins. This led to the discovery of many novel chemotypes showing a range of cytotoxic activities [8] including the taxanes and camptothecins, but their development into clinically active agents spanned a period of some 30 years, from the early 1960s to the 1990s. This plant collection program was terminated in 1982, but the development of new screening technologies led to the revival of collections of plants and other organisms in 1986, with a focus on the tropical and sub-tropical regions of the world. It is interesting to note, however, that no new plant-derived clinical anti-cancer agents have, as yet, reached the stage of general use, but some agents are in preclinical development.

Plant-Based Anticancer Drugs:

1. Vinka Alkaloid: Vinka alkaloids are anti-mitotic and anti-microtubule alkaloid agents initially derived from the periwinkle plant *Catharanthus roseus* (basionym *Vinca rosea*) and other vinca plants. Vinca alkaloids are used in chemotherapy for cancer. They are a class of cell cycle–specific cytotoxic drugs that work by inhibiting the ability of cancer cells to divide: Acting upon tubulin; they prevent it from forming into microtubules, a necessary component for cellular division. Vinka alkaloid includes- Vinblastine (VLB) and Vincristine (VCR), Vinorelbine (VRLB) and Vindesine (VDS) are obtained from the *Catharanthus roseus* G. Don. (Apocynaceae).

Vincristine: Vincristine knew as leurocristine, sometimes abbreviated "VCR," is a vinca alkaloid from the *Catharanthus roseus* (Madagascar periwinkle), formerly *Vinca rosea* and hence its name. Vincristine's blockage of microtubule formation is especially powerful. The reason for this comes from the fact that tubulin protein is dynamic. Its long chain of building blocks is always growing in some places and breaking in others. The less contiguous parts of a tubulin molecule have pieces only two building blocks long, called dimers. Vincristine has a high affinity for tubulin dimers, and the reaction between vincristine and the dimers is rapidly reversible. That means a vincristine molecule will attach to a dimer at one site, break off, and then reattach at another site. This keeps two sites per dimer "poisoned" and unable to reassemble into the protein. So vincristine's ability to destabilize tubulin is especially good.

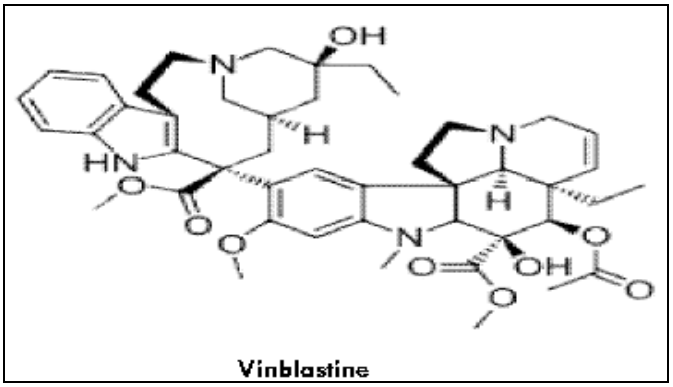


Vincristine: Disruption of the microtubules arrests mitosis in metaphase. Therefore, the vinca alkaloids affect all rapidly dividing cell types

including cancer cells, but also those of intestinal epithelium and bone marrow. The main side-effects of vincristine are peripheral neuropathy, hyponatremia, constipation, and hair loss.

Vincristine is delivered *via* intravenous infusion for use in various types of chemotherapy regimens. Its main uses are in non-Hodgkin's lymphoma as part of the chemotherapy regimen CHOP, Hodgkin's lymphoma as part of MOPP, COPP, BEACOPP, or the less popular Stanford V chemotherapy regimen, in acute lymphoblastic leukemia, and in treatment for nephroblastoma (Wilms tumor, a kidney tumor most common in young children). It is used in combination with prednisone to treat childhood leukemia.

Vinblastine: Vinblastine (VLB) is a naturally occurring active compound. Vinblastine sulfate is the salt of an alkaloid extracted from *Vinca rosea* Linn., a common flowering herb known as the periwinkle (more appropriately known as *Catharanthus roseus* G. Don). Previously, the generic name was vinca leukoblastine, abbreviated VLB. It is a stathmo kinetic oncolytic agent. When treated in vitro with this preparation, growing cells are arrested in metaphase. Vinblastine should not be given intramuscularly, subcutaneously or intra thecally.



Microtubule disruptive drugs like vinblastine, colcemid, nocodazole have been reported to act by two mechanisms. At very low concentrations they suppress microtubule dynamics, and at higher concentrations they reduce microtubule polymer mass. Vinblastine includes adverse effects are nausea and vomiting which usually lasts less than 24 hours, stomach pain, constipation, diarrhea, jaw pain, headache, or another ache, thinned or brittle hair, exposed areas of the skin may become easily sunburned. Vinblastine is an anti-cancer medication prescribed in various cancers such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, breast cancer, testicular cancer, mycosis fungoides, Kaposi's sarcoma related to acquired immunodeficiency syndrome (AIDS), Letterer-Siwe disease. Vinblastine is also used to treat non-small cell lung cancer, bladder cancer, head and neck cancer, cervical cancer, idiopathic thrombocytopenia purpura, and autoimmune hemolytic anemia. Vinblastine sulphate is contraindicated in patients who are leucopenia. It should not be used in the presence of bacterial infection. Such infections should be brought under control.

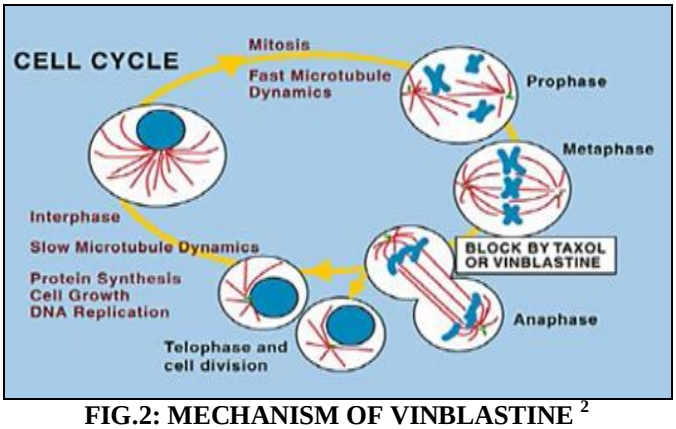
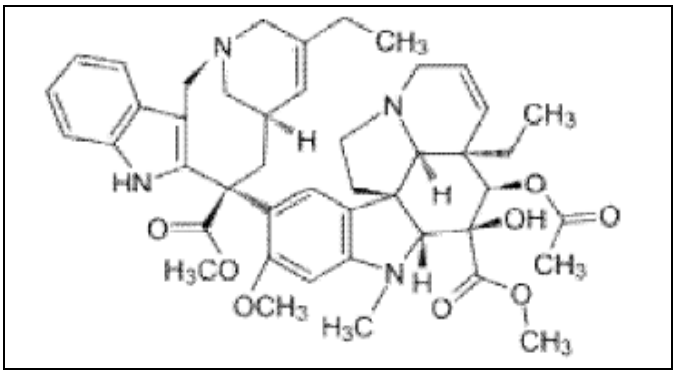


FIG.2: MECHANISM OF VINBLASTINE [2]

Vinorelbine: Vinorelbine is the first 5´NOR semi-synthetic vinca alkaloid. It is obtained from alkaloids from the rosy periwinkle, *Catharanthus roseus*. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Vinorelbine binds to the microtubular proteins of the mitotic spindle, leading to crystallization of the microtubule and mitotic arrest or cell death. Like other vinca alkaloids, vinorelbine may also interfere with:

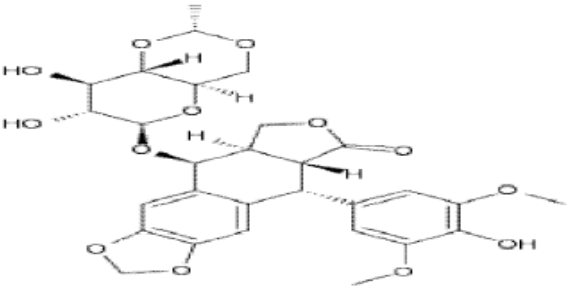


Vinorelbine Amino acid, cyclic AMP, and glutathione metabolism, 2) calmodulin dependent Ca2+-transport ATPase activity, 3) cellular respiration, and 4) nucleic acid and lipid biosynthesis. Adverse effects of vinorelbine are Lowered resistance to infection, bruising or bleeding, anemia, constipation, diarrhea, nausea, numbness or tingling in hands or feet (peripheral neuropathy), tiredness and a general feeling of weakness (asthenia), inflammation of the vein into which it was injected (phlebitis). Seldom severe hyponatremia is seen. Less common effects are hair loss and allergic reaction. Vinorelbine is approved for the treatment of non-small cell lung cancer and metastatic breast cancer. It is also active in rhabdomyosarcoma. Administration of Vinorelbine is contraindicated in patients with pretreatment granulocyte counts <1,000 cells/ mm^3.

2. Epipodophyllotoxin: The most studied lignan, podophyllotoxin, and its semisynthetic derivatives (etoposide, teniposide, etoposide phosphate), are particularly impressive at a curative level due to their cytotoxic properties. These semi-synthetic derivatives are used in chemotherapy of lung cancer. Podophyllin, an ethanolic extract of *Podophyllum peltatum* L. or *P. emodi* Wall (syn. *P. hexandnum* Royle), is a good source of the aryltetralin-type lignan, podophyllotoxin.

Etoposide: Etoposide phosphate is an anticancer agent, which belongs to the drug type topoisomerase inhibitor**.** Etoposide forms a ternary complex with DNA and the topoisomerase II enzyme (which aids in DNA unwinding), prevent re-ligation of the DNA strands, and by doing so causes DNA strands to break.

Adverse effects of etoposide include low blood pressure, hair loss, pain and or burning at the IV site, constipation or diarrhea, metallic food taste, Bone marrow suppression, leading to decreased white blood cell counts (leading to increased susceptibility to infections), low red blood cell counts (anemia), low platelet counts (leading to easy bruising and bleeding), nausea and vomiting, allergic-type reactions, rash, fever often occurring shortly after IV administration and not due to infection, mouth sores, acute myeloid leukemia (which ironically can be treated with etoposide itself).

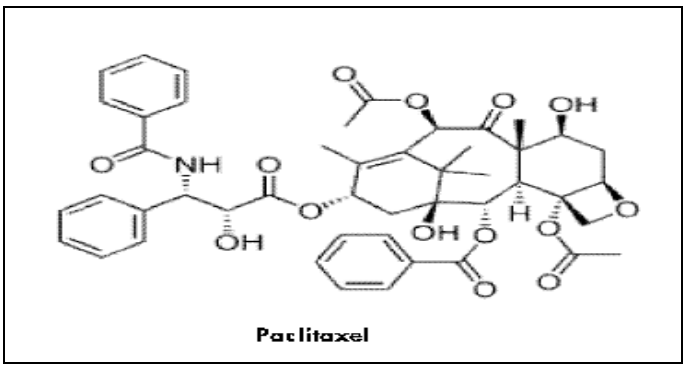


Etoposide phosphate

Etoposide is used as a form of chemotherapy for cancers such as Kaposi's sarcoma, Ewing's sarcoma, lung cancer, testicular cancer, lymphoma, nonlymphocytic leukemia, and glioblastoma multiforme. It is also sometimes used in a conditioning regimen before a bone marrow or blood stem cell transplant. Etoposide contraindicated In Hypersensitivity, pregnancy, lactation.

3. Taxanes: The prototype taxane is the natural product paclitaxel, known initially as Taxol and first derived from the bark of the Pacific Yew tree. Docetaxel is a semi-synthetic analog of paclitaxel. Taxanes enhance the stability of microtubules, preventing the separation of chromosomes during anaphase.

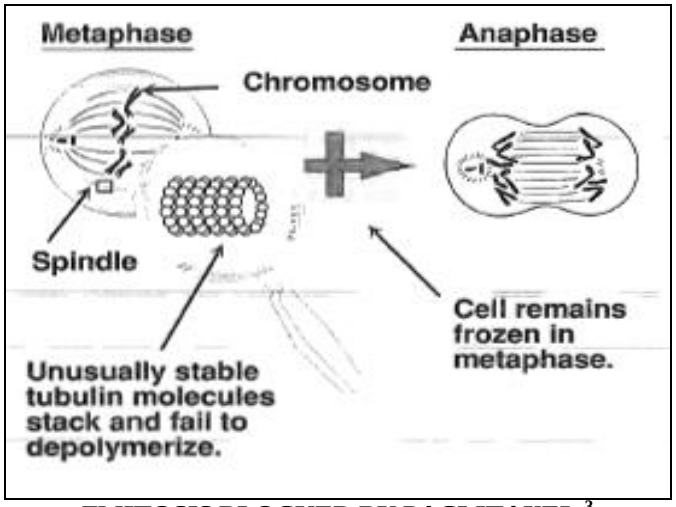
Paclitaxel: A cyclohexane isolated from the bark of the Pacific yew tree, *Taxus brevifolia*. It stabilizes microtubules in their polymerized form leading to cell death.



Paclitaxel

Paclitaxel interferes with the normal function of microtubule growth. Paclitaxel binds to the β subunit of tubulin. Tubulin is the "building block" of microtubules, and the binding of paclitaxel locks these building blocks in place. The resulting micro-tubule/paclitaxel complex cannot disassemble.

This adversely affects cell function because the shortening and lengthening of microtubules (termed dynamic instability) are necessary for their function as a transportation highway for the cell. Further research has indicated that paclitaxel induces programmed cell death (apoptosis) in cancer cells by binding to an apoptosis stopping protein called Bcl-2 (B-cell leukemia 2) and thus arresting its function.



FMITOSIS BLOCKED BY PACLITAXEL [3]

Common side effects include nausea and vomiting, loss of appetite, change in taste, thinned or brittle hair, pain in thejoints of the arms or legs lasting two to three days, changes in the color of the nails, and tingling in the hands or toes. More serious side effects such as unusual bruising or bleeding, pain/redness/swelling at the injection site, change in normal bowel habits for more than two days, fever, chills, cough, sore throat, difficulty swallowing, dizziness, shortness of breath, severe exhaustion, skin rash, facial flushing, female infertility by ovarian damage and chest pain canalso occur.

A number of these side effects are associated with the excipient used, Cremophor EL, a polyoxyethylatedcastor oil. Allergies to drugs such as cyclosporine, teniposideand drugs containing polyoxyethylated castor oil may indicate they increased the risk of adverse reactions to paclitaxel. Paclitaxel is approved for ovarian, breast and lung cancers and Kaposi's sarcoma. Paclitaxel should be available for the treatment of advanced breast cancer after the failure of anthracyclic chemotherapy, but that its first-lineuse should be limited to clinical trials.

Paclitaxel is contraindicated in patients with severe hypersensitivity to paclitaxel or any excipient, especially macrogolglycerolricinoleate (polyoxy-ethylated castor oil). Paclitaxel is contraindicated during pregnancy and lactation, and should not be used in patients with baseline neutrophils < 1,500/mm³ (<1,000/mm³ for KS patients). In KS, paclitaxel is also contraindicated in patients with concurrent, severe and uncontrolled infection.

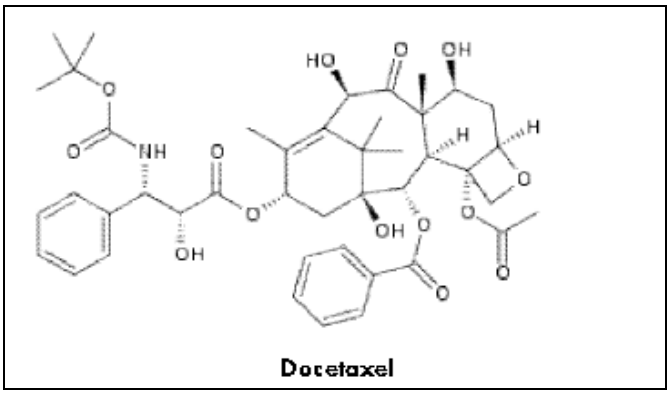
TABLE 1: PLANT BASED ANTICANCER AGENTS IN CLINICAL PRACTICE.

Compounds	Uses	Status
Vincristine	Leukemia, lymphoma, breast, lung, pediatric solid cancers and others	Phase III/IV
Vinblastine	Breast, lymphoma, germ-cell and renal cancer	Phase III/IV
Vinorelbine	Lymphoma, tumors, Lung cancer	Phase I-III
Paclitaxel	Ovary, breast, lung, bladder and head and neck cancer	Phase III/IV
Docetaxel	Breast and lung cancer	Phase III
Topotecan	Ovarian, lung and pediatric cancer	Phase II/III

Docetaxel: Docetaxel (as generic or under the trade name Taxotere) is a well-established anti-mitotic chemotherapy medication (that is, it interferes with cell division). The cytotoxic activity of docetaxel is exerted by promoting and stabilizing microtubule assembly while preventing physiological microtubule depolymerization/disassembly in the absence of GTP. This leads to a significant decrease in free tubulin, needed for microtubule formation and results in inhibition of mitotic cell division between metaphase and anaphase, preventing further cancer cell progeny. Because microtubules do not disassemble in the presence of docetaxel, they accumulate inside the cell and cause initiation of apoptosis.

Apoptosis is also encouraged by the blocking of apoptosis-blocking bcl-2oncoprotein. Both *in vitro* and *in-vivo* analysis show the antineoplastic activity of docetaxel to be effective against a wide range of known cancer cells, cooperate with other antineoplastic agents activity, and have greater cytotoxicity than paclitaxel, possibly due to its more rapid intracellular uptake. This includes tumor cells as well as hair follicles, bone marrow, and other germ cells. For this reason, common chemotherapy side effects such as alopecia occur; sometimes this can be permanent.

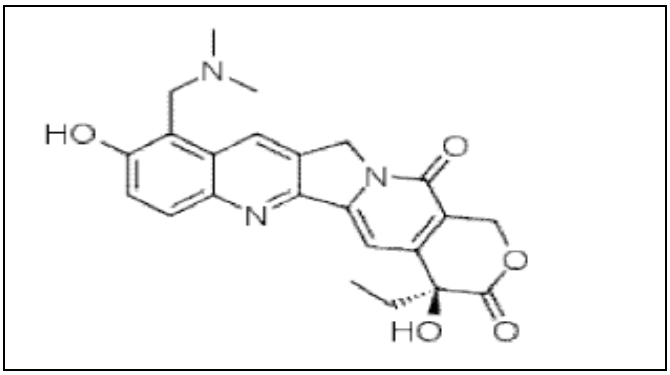
Hematological adverse effects include Neutropenia (95.5%), Anemia (90.4%), febrile neutropenia (11.0%) and thrombocytopenia (8.0%).The main use of docetaxel in the treatment of a variety of cancers after the failure of anthracycline-basedchemotherapy [4]. Marketing of docetaxel as Taxotere is mainly towards the treatment of breast, prostate, and other non-small cell cancers[5]. Clinical data has shown docetaxel to have cytotoxic activity against breast, colorectal, lung, ovarian, prostate, liver, renal, gastric, head and neck cancers, and melanoma. Docetaxel is contraindicated for use with patients with; a baseline neutrophil counts less than 1500 cells/µL, a history of severe hypersensitivity reactions to docetaxel or polysorbate 80, severe liver impairment, and pregnant or breastfeeding women.



Docetaxel

4. Camptothecins: Camptothecin (CPT) is a cytotoxic quinoline alkaloid which inhibits the DNA enzyme topoisomerase I (topo I). It was discovered in 1966 by M. E. Wall and M. C. Wani in the systematic screening of natural products for anticancer drugs. It was isolated from the bark and stem of *Camptotheca acuminata* (Camptotheca, Happy tree), a tree native to China used as a cancer treatment in Traditional Chinese Medicine.

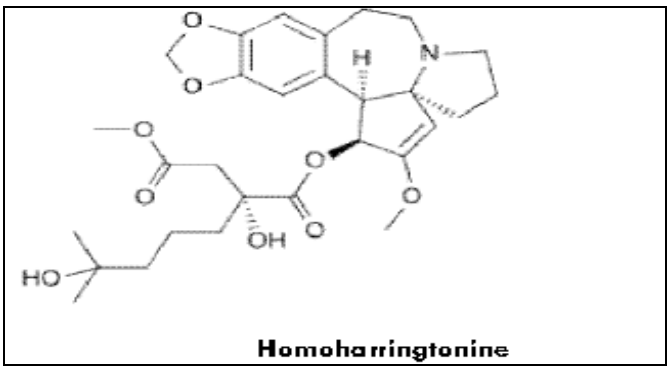
Topotecan: Topotecan (trade name Hycamtin) is a chemotherapeutic agent that is a topoisomerase inhibitor. It is a water-soluble derivative of camptothecin. It's brand name is Hycamptamine, Hycamptin, Hycamtin. Topotecan has the same mechanism of action as irinotecan and is believed to exert its cytotoxic effects during the S phase of DNA synthesis. Topoisomerase I relieves torsional strain in DNA by inducing reversible single-strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single-strand breaks. This ternary complex interferes with the moving replication fork, which leads to the induction of replication arrest and lethal double-stranded breaks in DNA.



Topotecan: As mammalian cells cannot efficiently repair these double-strand breaks, the formation of this ternary complex eventually leads to apoptosis (programmed cell death). Side effects include Myelosuppression, Diarrhea, Low blood counts, Susceptibility to infection. Topotecan is used to treat patients with metastatic cancer (cancer that has already spread) of the ovaries after other treatments have failed. This medicine is also used to treat a certain type of lung cancer called small cell lung cancer. It is also used in combination with cisplatin to treat cancer of the cervix which cannot be treated with surgery or radiation therapy.

5. Cephalotaxanes: Cephalotaxus [*C. harringtonia* and *C. fortuni*]-source of harringtonine, it is a promising new anti-cancer alkaloid.

Homoharringtonine: Omacetaxinemepesuccinate (INN, or homoharringtonine, trade name Omapro) is an alkaloid from *Cephalotaxus harringtonia* that is investigated for potential use as a drug against hematological cancers. It is being developed by Chem Genex and is on fast track approval schedule in the United States. Omacetaxine has been granted orphan drug status in the U.S. and Europe.

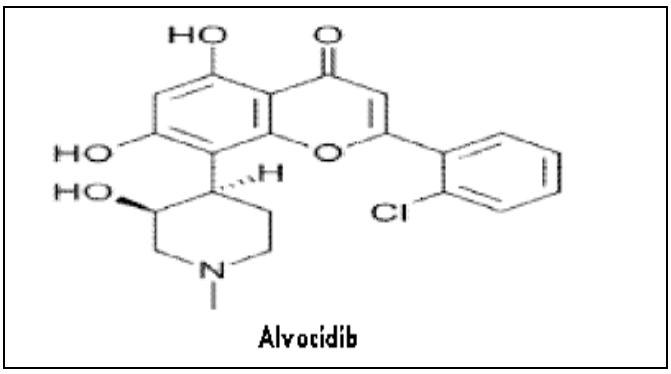


Homoharringtonine

Omacetaxine induces apoptosis by inhibition of protein synthesis, particularly Mcl-1. It has a different point of action than tyrosine kinase inhibitors like imatinib and has potential therapeutic advantages for patients who have developed resistance to tyrosine kinase inhibitor therapy. Nausea and vomiting, diarrhea, and fever and chills were the most common side effects. Serious reversible cardiovascular toxicity, which occurred in three patients, included symptomatic hypotension in two and short runs of ventricular tachycardia in one. Use in sarcoma and breast cancer as well as in ovarian and endometrial carcinoma, in solid tumors, in myeloid leukemia, myelodysplastic syndrome, acute promyelocytic leukemia, and, most important, chronic myeloid leukemia (CML).

6. Flavones: In recent years, flavonoids and their synthetic analogs have been intensely investigated in the treatment of ovarian, breast, cervical, pancreatic, and prostate cancer.

Flavopiridol (Alvocidib): Rohitukine ($C_{16}H_{19}O_5N$), a chromane alkaloid, was first reported from *Amoora rohituka* (Roxb.) Wight & Arn. And then from *Dysoxylum binectariferum* Hook both from the family Meliaceae. Alvocidib (also known as Flavopiridol HMR-1275) is a cyclin-dependent kinase inhibitor under clinical development for the treatment of chronic lymphocytic leukemia. It has also been studied for the treatment of arthritis. A phase I/II study of Flavopiridol to treat relapsed mantle cell lymphoma or diffuse large B-cell lymphoma has been completed.



Alvocidib

Alvocidib inhibits cyclin-dependent kinases, arresting cell division and causing apoptosis in non-small lung cancer cells. Main side effects were secretory diarrhea and a pro-inflammatory syndrome associated with hypotension and investigated for use/treatment in esophageal cancer, leukemia (lymphoid), lung cancer and liver cancer.

Herbs and Anti-Oxidants that Fight with Cancer:

Garlic: The National Cancer Institute (affiliated to the NIH) recognizes garlic to have potential anticancer properties. The sulphydryl compounds in garlic can block the formation of cancer-causing substances. Several population studies have shown an association between increased garlic consumption and reduced risk of cancers of the stomach, colon, esophagus, pancreas, and also breast cancer. A study has found that garlic intake of 10 g per day could reduce the risk of prostate cancer by 50 percent.

Ginger: Some pungent substances present in ginger rhizome have anti-oxidant and anti-inflammatory activities. The anti-cancer properties of ginger are attributed to phenolic materials such as 6-gingerol and 6-paradol and other constituents such as shogaols and zingerone. A study published in the journal Biochemical and Biophysical Research Communications reported that 6-gingerol could reduce the viability of gastric cancer cells and limit the spread of cancer.

Turmeric: Although turmeric is promoted mainly as an anti-inflammatory herbal remedy, some scientists believe that the anti-oxidant curcumin present in turmeric may prevent or slow the growth of many cancers including tumor of esophagus, stomach and intestine, breast cancer and also skin cancer in experimental animals. However, clinical research is needed to determine its efficacy in cancer prevention and treatment in human beings. But, the laboratory studies have confirmed the curcumin interferes with several molecular pathways involved in cancer development, growth and spread. Further, a study found that ethanolic extract of turmeric produces remarkable symptomatic relief in patients with external cancerous lesions. There was a reduction in smell in 90 percent of cases and reduction in itching in almost all cases.

Green Tea: Polyphenols in green tea and sometimes black tea, help kill cancerous cells and

stop their progression. Mayo Clinic studies have revealed that a substance called epigallocatechin gallate (EGCG) in green tea reduces the number of leukemia cells in patients with CLL (Chronic lymphocytic leukemia), a form of blood cancer. Similarly, another study found that women who drank powdered green tea were less likely to develop bladder cancer. Again, men who drank the greenest tea were 37 percent less likely to develop pancreatic cancer. A large Chinese clinical study found.

Cilantro: Cilantro or, more commonly, coriander is another potent herb that has anti-cancer properties. The prevalent anti-oxidants in cilantro are beta-carotene, quercetin, and rutin. This herb, generally used in chelation therapy for people suffering from lead poisoning, helps remove free radicals by getting rid of the heavy metals in your body.

Basil: Basil is well known for its medicinal value. Apart from having anti-inflammatory, blood pressure lowering, and nervous system stimulating properties, this popular herb has been found to have the chemoprotective potential for colon cancer. A study found that basil played a significant role in reducing colon tumors in experimental animals. However, no human clinical trials have been conducted to confirm this experiment.

Survival of Plants used as Anticancer Agents: The World Health Organization estimates that approximately 80% of the world's inhabitants rely on traditional medicine for their primary health care [6]. The National Cancer Institute collected about 35,000 plant samples from 20 countries and has screened around 114,000 extracts for anticancer activity. From this screening two or three most important anti-cancer compounds available today, namelytaxol and camptothecin. Various types of anti-cancer plant are zedoary (*Curcuma zedoaria*), marijuana (*Cannabis sativa*), Indian trumpet (*Oroxylum Indicum*), celandine (*Chelidonium majus*), yew (*Taxus baccata*), turmeric (*Curcuma longa*), rodent tuber (*Typhoniumflagelliforme*), god's crown (*Phaleriama crocarpa*), madagaskar periwinkle (*Catharanthus rosens*), artocarpus integer (*Selaginella corymbosa*), bamboo grass (*Loathatreum gràcies*), handsome (*Taraxacum mongolicum*), fruit makasar (*Brucca javanica*), garlic (*Allium sativum*), echo china (*Smilax china*), sunflower (*Helianthus annus*), leunca (*Solanum nigrum*), job's tears (*Coix lachryma-Jobi*), bamboo rope (*Asparagus cochinchinensis*), acanthopanax root bark (*Acanthopanax gracilistylus*), licorice (*Glycyrrhiza glabra*) *etc*. A brief description of medicinal plants in Asian origin used for the prevention and treatment of cancer is given below. The review provides information on the active anticancer components of the plants.

Dietary Source of Anti-Cancer Agents: Natural dietary agents including fruits, vegetables, and spices have drawn a great deal of attention from both the scientific community and the general public owing to their demonstrated ability to suppress cancers. Recent studies suggest that the consumption of food rich in fruits, vegetables, and spices have a lower incidence of cancers (stomach, esophagus, lung, oral cavity and pharynx, endometrium, pancreas, and colon).

TABLE 2: PLANTS USED AS ANTI-CANCER

S. no.	Plant species	Family	Plant part
1	*Salvia officinalis*	Labiatae	Leaves [7]
2	*Viscum album*	Loranthaceae	Leaves [8]
3	*Combretum caffrum*	Combretaceae	Bark [9]
4	*Melaleuca alternifolia*	Myrtaceae	Leaves [10]
5	*Lavandula angustifolia*	Labiatae	Leaves [10]
6	*Aglaia foveolata*	Meliaceae	Fruit [11]
7	*Maytenus serrata*	Celastraceae	Seed [12]
8	*Tabebuia impetiginosa*	Bignoniaceae	Stem bark and trunk wood [13, 14]
9	*Tabebuia rosea*	Bignoniaceae	Stem bark and trunk wood [13, 14]
10	*Tabebuia serratifolia*	Bignoniaceae	Stem bark and trunk wood [13, 14]
11.	*Dipteryx odorata*	Fabaceae	Seed [15]
12	*Thapsia garganica*	Apiaceae	Fruit [16]
13	*Indigo feratinctoria*	Leguminosae	Aerial part [17]
14	*Matricaria chamomilla*	Asteraceae	Flower [18]

15	*Erythroxylum pervillei*	Erythroxylaceae	Root [19]
16	*Broussonetia papyrifera*	Urticaceae	Entire [20]
17	*Cyclopia intermedia*	Fabaceae	Leaves [21]
18	*Scutellariae radix, Scutellariae indica*	Labiatae	Root [23]
19	*Physalis philadelphica*	Solanaceae	Seed [23]
20	*Dysoxylum binectariferum*	Meliaceae	Stem bark [24]
21	*Aristotelia chilensis*	Elaeocarpaceae	Leaf and Stem [25]
22	*Cyathostemma argentium*	Annonaceae	Root [26]
23	*Epimedium hunanense*	Berberidaceae	Aerial parts [27]
24	*Croton urucurama*	Euphorbiacaeae	Bark [28]
25	*Epilobium hirsutum*	Onagraceae	Entire [29]
26	*Pleione bulbocodioides*	Orchidaceae	Tuber [30]
27	*Cassia quinquangulata*	Caesalpiniaceae	Root [31]
28	*Begonia glabra*	Begoniaceae	Entire [32]
29	*Celastrus orbiculatus*	Celastraceae	Entire [32]
30	*Croton draco*	Euphorbiacaeae	Aerial parts [33]
31	*Smilax sieboldii*	Liliaceae	Entire [33]
32	*Ximenia Americana*	Olacaceae	Root [33]
	Lymphoma (unspecified)		

TABLE 3: ANTICANCER AGENT DERIVED FROM DIETARY SOURCES

S. no.	Botanical Name	Source	Compound
1	*Carica papaya*, Family- Caricaceae	Berries	β-Cryptoxanthin [34]
2	*Glycyrrhiza glabra; Glycyrrhiza radix; Glycyrrhiza uralensis*; Family: Leguminosae	Licorice root	Glycyrrhizin [35]
3	*Cannabis sativa*; Family: Cannabiaceae	Hemp	Cannabinol [36]
4	*Rosamarinus officinalis*; Family: Lamiaceae	Rosemary	Carnosol [37]
5	*Glycine max*; Family: Fabaceae	Soybeans	Genistein [38]
6	*Prunus armeniaca*; Family: Rosaceae	Apricots	Carotenoids [39]
7	*Zingiber officinale*; Family: Zingiberaceae	Tuber	Gingerol [40]
8	*Lycopersicon esculentum*; Family: Solanaceae	Tomato	Lycopene, Lutein, Kaempferol [40]
9	*Piper nigram; Piper longum*; Family: piperaceae	Black pepper	Purpurogallin; Piperine [41]
10	*Ocimum sanctum*; Family: Lamiaceae	Basil	Ursolic acid [42]
11.	*Betula alba*; Family: Betulaceae	Birch tree	Betulinic acid [43]
12	*Crocus sativus*; Family: Iridaceae	Saffron	Carotenoids [44]
13	*Silymarin marianum*; Family: Asteraceae	Milk thistle	Silymarin [45]
14	*Capsicum annum; capsicum frutescans*; Family: Solanaceae	Red chilli	Capsaicinoids, Capsaicia [46]
15	*Camelia sinensis*; Family: Theaceae	Green and black teas	Catechin and flavins [47]
16	*Vitis vinfera*; Family: Vitaceae	Grapes	Resveratrol [48]
17	*Daucuscarota sativa*; Family: Apiaceae/ Umbelliferae	Carrot	β-Carotene [49]
18	*Tabebuia avellanedae*; Family: Bignoniaceae	Lapacha tree	Lapachone
19	*Citrus Aurantium*; Family: Rutaceae	Orange	Hesperidin [50]
20	*Prunus dulcis*, Family- Rosaceae	Almond	Morin [51, 52]
21	*Aloe arborescens*; Family: Asphodelaceae	Aloe vera	Emodin [53]
22	*Opium poppy*; Family: Papaveraceae	Poppy	Morphine and its analogs [54]
23	*Cucurbita moschata*; Family: Cucurbitaceae	Pumpkin	β-Carotene [54]
24	*Azadirachata indica*; Family: Meliaceae	Neem	Polyphenolics [55]

Dietary derivatives consist of a wide variety of biologically active components that are responsible for the anti-cancer properties. Examples- are curcumin, genistein, resveratrol, diallyl sulfide, S-allyl cysteine, allicin, lycopene, capsaicin, diosgenin, gingerol, ellagic acid, ursolic acid, silymarin, anethol, catechins, eugenol, isoeugenol, dithiolthiones, isothiocyanates, indole-3-carbinol, isoflavones, saponins, phytosterols, inositol hexaphosphate, vitamin C, D-limonene, lutein, folic acid, beta carotene, selenium, vitamin E and flavonoids. Many of which have been used in traditional medicines for thousands of years. These dietary agents are believed to suppress the

inflammatory processes that lead to transformation, hyperproliferation, and initiation of carcinogenesis. Their inhibitory influences may ultimately contain the final steps of carcinogenesis *i.e.* angiogenesis and metastasis.

CONCLUSION: Natural products are a prime source for the treatment of many forms of cancer, many of which are consumed daily with the diet. They provide significant protection against various cancers and many other diseases. The antioxidant medicinal plants and their products prevent the cancer and other diseases by protecting cells from damage. Thus, consuming a diet rich in antioxidant fruits, vegetables, herbs, *etc*. will provide health-protective effects. All the natural products discussed in this review exhibit anticancer activities. Natural products offer an excellent opportunity to evaluate not only new chemical classes of anticancer agents, but also novel and potentially relevant mechanisms of action.

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