International Journal of Research and Development in Pharmacy and Life Sciences
Available online at http//www.ijrdpl.com
February - March, 2013, Vol. 2, No.2, pp 293-308
ISSN: 2278-0238

Review Article

PLANT DERIVED ANTICANCER AGENTS: A REVIEW

Preeti Singh Sisodiya

Swami Vivekanand College of Pharmacy, Indore- 452020, India

(Received: October 19, 2012; **Accepted:** January 13, 2013**)**

ABSTRACT

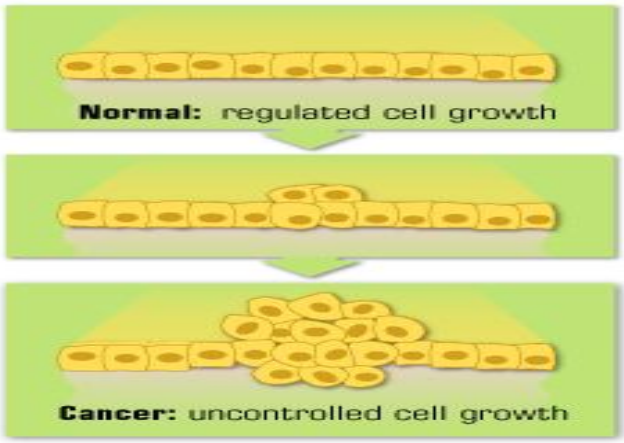
Cancer is a major public health burden in both developed and developing countries. Plant-derived compounds have been an important source of several clinically useful anti-cancer agents including taxol, vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, and etoposide derived from epipodophyllotoxin are in clinical use all over the world. About 30 plant derived compounds have been isolated so far and are currently under clinical trials. Cancer chemopreventive agents, many of which are natural products, are capable of preventing or inhibiting the process of carcinogenesis. As with other pharmaceutical agents useful for disease prevention, a pharmacoeconomic analysis of a cancer chemopreventive formulation would need to be considered, and the composition of the formulation should improve over time. A number of promising new agents are in clinical development based on selective activity against cancer-related molecular targets, including flavopiridol, roscovitine, combretastatin A-4 phosphate , betulinic acid and silvestrol are in clinical or preclinical development .

Keywords: Cancer, clinical trial, vinka alkaloid, epipodophyllotoxin, taxanes, camptothecine, cephalotaxanes, flavones, stilbenes.

INTRODUCTION

Cancer disease caused by an uncontrolled division of abnormal cells in a part of the body.. The cancer is very serious if the tumor begins to spread (metastasize) throughout the body. There are many different types of cancer. They are named based on where the tumor is located, or where it first started growing in the body. The most common forms of cancer are colon, lung, breast and prostate cancer.

Chemotherapyis the use of anti-cancer of drugs. Anti-cancer drugs destroy cancer cells by stopping growth or multiplication at some point in their life cycles. Drugs may be administered intravenously (into a vein), orally (by mouth), by injection into a muscle, topically (applied to the skin) or in other ways, depending on the drug and the type of cancer. Chemotherapy is often given in cycles of alternating treatment and rest periods. Radiation therapy is the treatment of cancer and other diseases with ionizing radiation. Ionizing radiation destroys cells, or the genetic material of cells, in the area being treated, thereby making it impossible for these cells to continue to grow.



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. As a result, the United States National Cancer Institute (NCI) initiated an extensive plant collection program in 1960, focused mainly in temperate regions. This led to the discovery of many novel chemotypes showing a range of cytotoxic activities (Cassady and Douros, 1980), 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 plantderived clinical anti-cancer agents have, as yet, reached the stage of general use, but a number of agents are in preclinical development.

PLANT DERIVED ANTICANCER DRUGS IN CLINICAL DEVELOPMENT

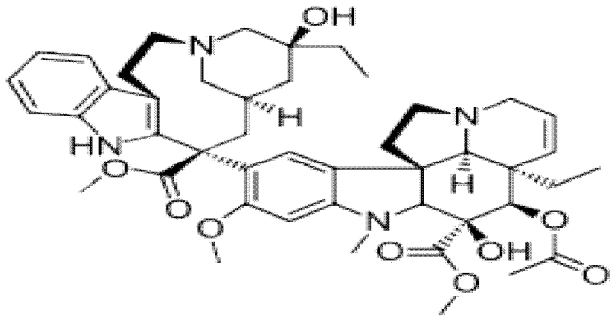
A. Vinka Alkaloid:

Vinca alkaloids belong to an important class of anti-cancer drugs. The mechanism of action of Vinca alkaloids is that they inhibit the cell proliferation by affecting the microtubular dynamics during mitosis, and this causes a characteristic block during mitosis leading to apoptosis. Vinka alkaloid include, Vinblastine (VLB) and Vincristine (VCR), Vinorelbine (VRLB) and Vindesine (VDS) are obtained from the Madagascar periwinkle, Catharanthus roseus G. Don. (Apocynaceae).

Catharanthus roseus

1. Vinblastine

Vinblastine (VLB) is major naturally occurring active compounds .Vinblastine sulfate is the salt of an alkaloid extracted from Vinca rosea Linn., a common flowering herb known as the periwinkle (more properly known as Catharanthus roseus G. Don). Previously, the generic name was vincaleukoblastine, abbreviated VLB. It is a stathmokinetic oncolytic agent. When treated in vitro with this preparation, growing cells are arrested in metaphase. Vinblastine should not be given intramuscularly, subcutaneously or intrathecally.



Vinblastine

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 polymer mass.

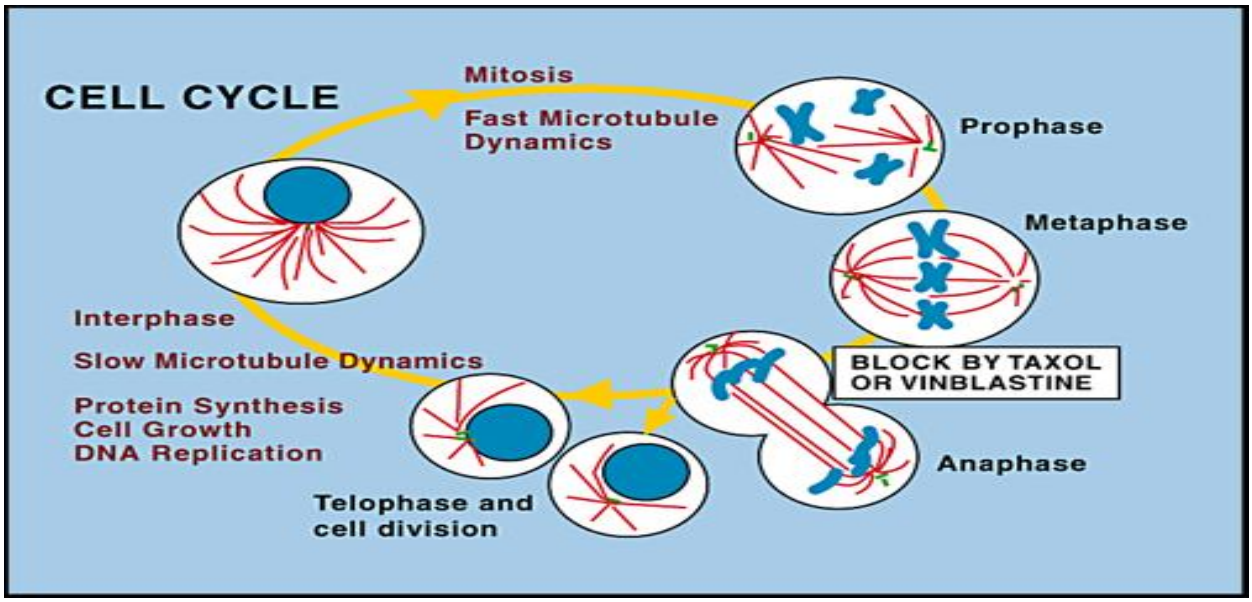
Vinblastine includes adverse effects are nausea and vomiting which usually lasts less than 24 hours, stomach pain, constipation, diarrhea, jaw pain, headache, or other ache, thinned or brittle hair, exposed areas of the skin may become easily sunburned.

Vinblastine is an anti-cancer medication prescribed in various cancers such as Hodgkins lymphoma, non Hodgkins 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 leucopenic. It should not be used in the presence of bacterial infection. Such infections should be brought under control with

Vinka alkaloid analogues in clinical trial

BINDING DOMAIN	RELATED DRUGS OR ANALOGUES	THERAPEUTIC USES	STAGE OF CLINICAL DEVELOPMENT
VINCA DOMAIN	VINBLASTINE	Hodgkin's disease, testicular germ cell cancer	in clinical use; 22 combination trials in progress
	VINCRISTINE	Leukaemia, lymphomas	In clinical use; 108 combination trials in progress
	VINORELBINE	Solid tumours, lymphomas, lung cancer	In clinical use; 29 phase I–IIIclinical trials in progress (single and combination)
	VINFLUNINE	Bladder, non-small-cell lung cancer, breast cancer	Phase III



Mechanism of vinblastine

Combinations with vinblastine in clinical trial

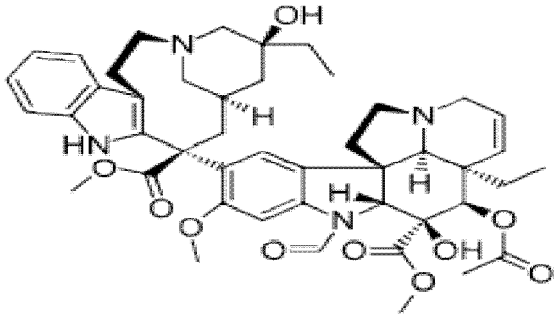
COMBINATION	USE
vinblastine, bleomycin, cisplatin, and etoposide (VBPE)	in children with primary intracranial germ cell tumors
cisplatin, bleomycin, and vinblastine (phase-3)	patients with metastatic testicular tumors
cisplatin (80 mg/m2, day 1), vinblastine (5 mg/m2, days 1 and 15), and ifosfamide (1.2 g/m2, days 1-3) (phase-2)	non-small-cell lung cancer
vinblastine and peptichemio	patients with metastatic breast cancer
Vinblastine and Chlorambucil (phase-2)	use in therapy of Hodgkin's Disease
Goserelin, Estramustine and Vinblastine (phase-2)	in Newly Diagnosed Metastatic Prostate Cancer
Vinblastine and rapamycin (phase-1)	synergistic inhibition of human neuroblastoma-related angiogenesis.

antiseptics or antibiotics before the initiation of therapy with vinblastine sulphate.

2. Vincristine:

Vincristine (brand name, Oncovin), formally known as **leurocristine**, sometimes abbreviated "VCR", is a vinca alkaloid from the Catharanthus roseus (Madagascar periwinkle), formerly Vinca rosea and hence its name. It is a mitotic inhibitor, and is used in cancer chemotherapy. Vincristine is created by the coupling of indole alkaloids vindoline and catharanthine in the vinca plant.

Vincristine



Tubulin is a structural protein that polymerizes to microtubules. The cell cytoskeleton and mitotic spindle, among other things, are made of microtubules. Vincristine binds to tubulin dimers, inhibiting assembly of microtubule structures. 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.

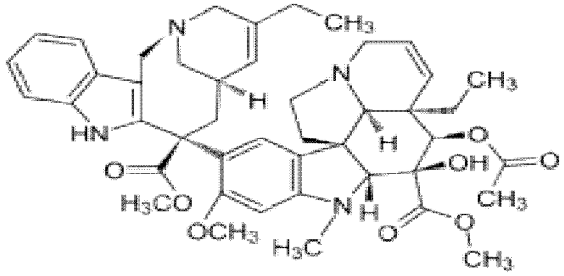
Vincristine is delivered via intravenous infusion for use in various types of chemotherapy regimens. Its main uses are in non-Hodgkin's lymphoma as part of the chemotherapy regimen CHOP, Hodgkin's lymphoma as part of MOPP, COPP, BEACOPP, or the less popular Stanford V chemotherapy regimen, in acute lymphoblastic 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. Vincristine hypersens to drug/class/compon.,intrathecal (IT) administration, acute bacterial infection, demyelinating Charcot-Marie-Tooth, GI obstruction, paralytic ileus, pregnancy, breastfeeding, caution if hepatic impairment, caution if bone marrow depression, caution if neuropathy, caution if neuromuscular dz, caution if concurrent neurotoxic agents, caution if concurrent ototoxic agents, caution if pulmonary dz.

Combinations with vincristine in clinical trial

COMBINATION	USE	TRIAL PHASE
Vincristine (VCR), cyclophosphamide (CP), and BCNU	in acute lymphocytic leukemia	
Topotecan and vincristine alone or in combination	childhood neuroblastoma , rhabdomyosarcoma , or brain tumors	phase II
cyclophosphamide, vincristine, and dacarbazine	advanced malignant pheochromocytoma	phase II
Bleomycin, Adriamycin, Cyclophosphamide, Vincristine, and Prednisone (BACOP)	in the Treatment of Advanced Diffuse Histiocytic Lymphoma	-
vincristine and prednisone.	malignant histiocytosis	-

3. Vinorelbine

Vinorelbine is the first 5′NOR semi-synthetic vinca alkaloid. It is obtained by semi-synthesis from alkaloids extracted from the rosy periwinkle, Catharanthus roseus. It is marketed in India by Abbott Healthcare under the brand name Navelbine.



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: 1) amino acid, cyclic AMP, and glutathione metabolism, 2) calmodulin-dependent Ca^{2+}-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, anaemia, constipation, diarrhoea, 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.

Combinations with vinorelbine in clinical trial

COMBINATION	USE	TRIAL PHASE
oral combination of vinorelbine/capecitabine	in patients with metastatic breast cancer	phase I
oral combination of vinorelbine with capecitabine	in patients with metastatic breast cancer	Phase II
Intravenous Vinorelbine in Combination With Epirubicin Versus Epirubicin Alone	in Patients With Advanced Breast Cancer	Phase III
docetaxel plus gemcitabine or vinorelbine	in refractory advanced breast cancer patients.	–

B. Epipodophyllotoxin

The most studied lignan, podophyllotoxin, and its semi-synthetic derivatives (etoposide, teniposide, etoposide phosphate), are particularly interesting 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.

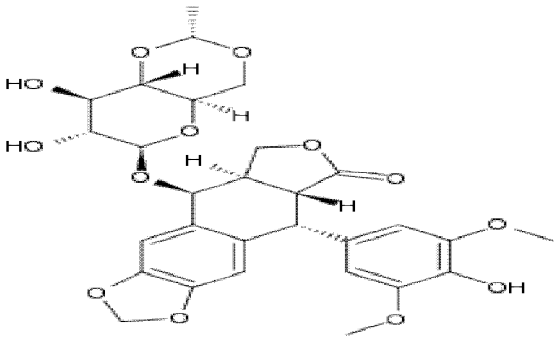
Podophyllum peltatum

Epipodophyllotoxin analogues in clinical trial

Name of analogue	Clinical status	Developer
NK-611	Phase I	Nippon Kayaku
Tafluposide 105	Phase I	Pierre Fabre

1. ETOPOSIDE:-

Etoposide phosphate (brand names: Eposin, Etopophos, Vepesid, VP-16) is an anticancer agent, which belongs to the drug type topoisomerase inhibitor.



Etoposide phosphate

Etoposide forms a ternary complex with DNA and the topoisomerase II enzyme (which aids in DNA unwinding), prevents 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 infectionmouth sores, Acute myeloid leukemia (which ironically can be treated with etoposide itself).

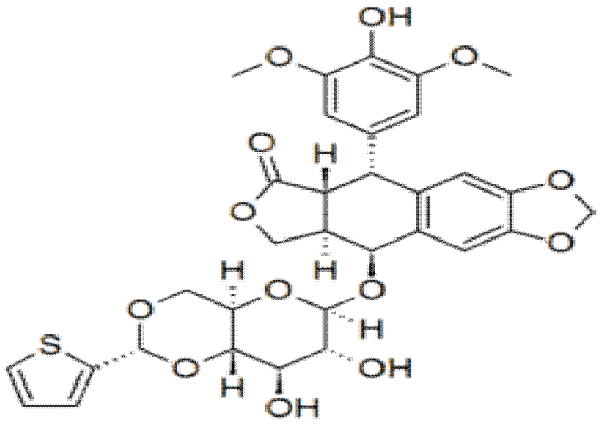
Etoposide is used as a form of chemotherapy for cancers such as Kaposi's sarcoma, Ewing's sarcoma, lung cancer, testicular cancer, lymphoma, nonlymphocytic leukemia, and glioblastoma multiforme. It is also sometimes used in a conditioning regimen prior to a bone marrow or blood stem cell transplant.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

Combinations wih etoposide in clinical trial

COMBINATION	USE
High-dose ifosfamide in combination with etoposide and epirubicin (IVE)	in the treatment of relapsed /refractory Hodgkin's disease and non-Hodgkin's lymphoma
Allosteric Akt Inhibitor MK-2206 with Etoposide or Rapamycin	Enhances the Antitumor Growth Effect inNeuroblastoma
Cisplatin and Etoposide	First-line Chemotherapy for Poorly Differentiated Neuroendocrine Carcinoma of the Hepatobiliary Tract and Pancreas
Bleomycin, etoposide, and cisplatin	ovarian granulosa cell tumors and other stromal malignancies.
Carboplatin (Paraplatin; JM8) and etoposide (VP-16)	first-line combination therapy for small-cell lung cancer.
etoposide 120 mg/m2 i.v. on day 1 and orally on days 2-5, adriamycin 40 mg/m2 i.v. on day 1 and vincristine 1.4 mg/m2 i.v. on day 1	patients with small cell carcinoma of the lung

2. Teniposide

A semisynthetic derivative of podophyllotoxin that exhibits antitumor activity. Teniposide inhibits DNA synthesis by forming a complex with topoisomerase II and DNA. This complex induces breaks in double stranded DNA and prevents repair by topoisomerase II binding. Accumulated breaks in DNA prevent cells from entering into the mitotic phase of the cell cycle, and lead to cell death. Teniposide acts primarily in the G2 and S phases of the cycle. It's brand name is Vee M-26, Veham-Sandoz, Vehem, Vumon.



Teniposide

The mechanism of action appears to be related to the inhibition of type II topoisomerase activity since teniposide does not intercalate into DNA or bind strongly to DNA. Teniposide binds to and inhibits DNA topoisomerase II. The cytotoxic effects of teniposide are related to the relative number of double-stranded DNA breaks produced in cells, which are a reflection of the stabilization of a topoisomerase II-DNA intermediate. Teniposide, when used with other chemotherapeutic agents for the treatment of ALL, results in severe myelosuppression. Other common side effects include gastrointestinal toxicity, hypersensitivity reactions, and alopecia. Teniposide used to treat childhood acute lymphocytic leukemia. VUMON is generally contraindicated in patients who have demonstrated a previous hypersensitivity to teniposide and/or Cremophor® EL (polyoxyethylated castor oil).

Combinations with teniposide in clinical trial

COMBINATION	USE
Teniposide and cytarabine	in the treatment of relapsed adolescent and adult acute lymphoblastic leukemia
cisplatin or carboplatin in combination with teniposide and vincristine	in the induction chemotherapy of small-cell lung cancer
methotrexate and teniposide infusions prior to reinduction therapy	in relapsed childhood acute lymphoblastic leukemia

(Phase II study)	
nimustine and teniposide [previous trial (NOA-01)]	in previously untreated glioblastoma (GBM).

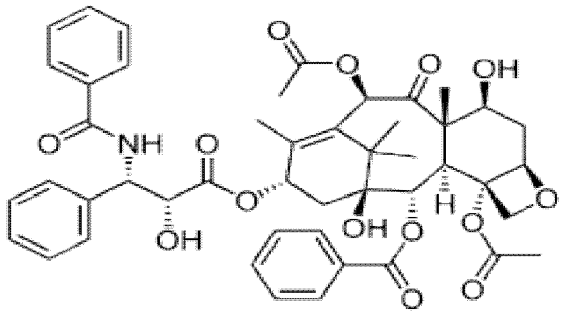
C. Taxanes

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

Bark of the Pacific Yew

1. Paclitaxel

A cyclodecane isolated from the bark of the Pacific yew tree, Taxus brevifolia. It stabilizes microtubules in their polymerized form leading to cell death. [PubChem] ABI-007 (Abraxane) is the latest attempt to improve upon paclitaxel, one of the leading chemotherapy treatments. It's brand name is Abraxane , Abraxis ,Bioscience, Epitaxol, Onxol ,Paxceed, Paxene ,Taxol ,Taxol A , Vascular Wrap , Xorane.



Paclitaxel

Paclitaxel / Taxol Analogues In Clinical Trials

Name of analogue	Clinical status	Developer
ABI-007 (suspension	Phase III	American Biosciences
BMS-188797	Phase II	Bristol–Myers Squibb
BMS-184476	Phase II	Bristol–Myers Squibb
BMS-275183	Phase I/II	Bristol–Myers Squibb
DHA-paclitaxel	Phase III	Luitpold
DJ-927	Phase II	Daiichi–Sankyo
MAC-321 (TL-00139)	Phase II	Wyeth/Taxolog
MST-997 (TL-909)	Phase I	Wyeth/Taxolog
Ortataxel (IDN-5109, BAY-59-8862)	Phase II	Bayer/Indena
Paclitaxel poliglumex (Xyotav)	Phase III	Cell Therapeutics
PNU-166945 (Taxol-HMPA polymer	Phase I	Pfizer
RPR-116258A	Phase III	Sanofi-Aventis
TPI-287	Phase II	Tapestry Pharmaceuticals
TXD-258 (XRP-6258, RPR-116258A)	Phase IIa	Sanofi-Aventis
XRP_9881 (RPR-109881 A)	Phase III	Sanofi-Aventis

Paclitaxel interferes with the normal function of microtubule growth. paclitaxel binds to the β subunit of tubulin. Tubulin is the "building block" of mictotubules, and the binding of paclitaxel locks these building blocks in place. The resulting microtubule/paclitaxel complex does not have the ability to disassemble. This adversely affects cell function because the shortening and lengthening of microtubules (termed dynamic instability) is 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. Common side effects include nausea and vomiting, loss of appetite, change in taste, thinned or brittle hair, pain in the joints 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 can

also occur. A number of these side effects are associated with the excipient used, Cremophor EL, a polyoxyethylated castor oil. Allergies to drugs such as cyclosporine, teniposide and drugs containing polyoxyethylated castor oil may indicate increased risk of adverse reactions to paclitaxel.[41] Dexamethasone is given prior to beginning paclitaxel treatment to mitigate some of the side effects.

Paclitaxel is approved in the UK 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-line use should be limited to clinical trials.

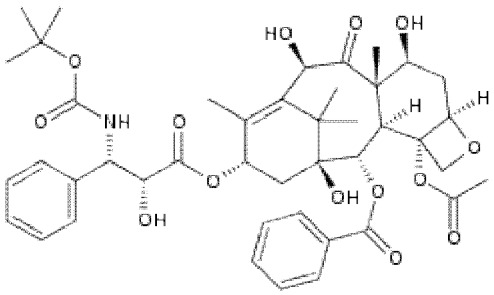
Paclitaxel is contraindicated in patients with severe hypersensitivity to paclitaxel or to any excipient, especially macrogolglycerol ricinoleate (polyoxyethylated castor oil). Paclitaxel is contraindicated during pregnancy and lactation (see section 4.6), and should not be used in patients with baseline neutrophils < 1,500/mm³ (<1,000/mm³ for KS patients). In KS, paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections.

Combinations with paclitaxel in clinical trial

Combination	Use	Trial phase
Doxorubicin and Paclitaxel	Front-Line Chemotherapy for Metastatic Breast Cancer	Phase III
paclitaxel and carboplatin	ovarian or lung cancer	-
Gefitinib in combination with paclitaxel and carboplatin	in advanced non-small-cell lung cancer	phase III
Trastuzumab, Paclitaxel, and Carboplatin Compared With Trastuzumab and Paclitaxel	in Women With HER-2–Overexpressing Metastatic Breast Cancer .	phase III

2. Docetaxel

Docetaxel (as generic or under the trade name Taxotere) is a clinically well-established anti-mitotic chemotherapy medication (that is, it interferes with cell division). The cytotoxic activity of docetaxel is exerted by promoting and stabilising microtubule assembly, while preventing physiological microtubule depolymerisation/disassembly in the absence of GTP.



Docetaxel

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-2 oncoprotein. Both in vitro and in vivo analysis show the anti-neoplastic activity of docetaxel to be effective against a wide range of known cancer cells, cooperate with other anti-neoplastic agents activity, and have greater cytotoxicity than paclitaxel, possibly due to its more rapid intracellular uptake.

This includes tumour 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. Haematological adverse effects include Neutropenia (95.5%), Anaemia (90.4%), Febrile neutropenia (11.0%) and Thrombocytopenia (8.0%).

The main use of docetaxel is the treatment of a variety of cancers after the failure of anthracycline-based chemotherapy.[4] Marketing of docetaxel as Taxotere is mainly towards the treatment of breast, prostate and other non-small cell cancers.[7] 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 count less than 1500 cells/μL, a history of severe hypersensitivity reactions to docetaxel or polysorbate 80, severe liver impairment and pregnant or breast-feeding women.

Common and/or likely drug-drug combination and known side effects from drug interactions

Drug Interacting with Docetaxel	Adverse Effects from Interaction
Cisplatin	increased risk of delayed neuropathy
Cyclosporine, Dalfopristin, Erythromycin, Itraconazole, Ketoconazole, Quinupristin, Terfenadine, Troleandomycin	increased risk of docetaxel toxicity including some or all of; anaemia, leucopoenia, thrombocytopenia, fever, diarrhoea
Doxorubicin Hydrochloride	cholestatic jaundice and pseudomembranous colitis
Doxorubicin Hydrochloride Liposome	increased doxorubicin exposure
Vaccinations for; Bacillus of Calmette and Guerin, Measles, Mumps, Poliovirus, Rotavirus, Rubella, Smallpox, Typhoid, Varicella, Yellow Fever	increased risk of infection by live vaccine
Thalidomide	increased risk of venous thromboembolism

D. 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 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.

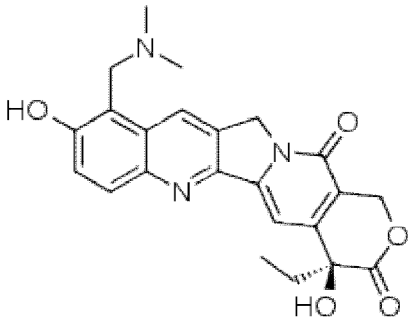
Camptotheca acuminata

Camptothecin analogues in clinical trials:-

Name of analogue	Clinical status	Developer
9-amino camptothecin	Phase III	Pharmacia
BN-80927	Phase I	Ispen/Roche
Diflomotecan (BN-80915) 100	Phase II	Ipsen
DRF-1042	Phase II	Dr Reddy
Exatecan mesilate	Phase III	Daiichi Pharmaceuticals
Gimatecan (ST-1481)	Phase II	Novartis/Sigma-Tau
Irinotecan (Hycamp)	Phase IIb	Meditech's & Alchemia
KarenitecinW (BNP-1350)	Phase I/II	BioNumerik
LE-SN38	Phase I/II	Neo Pharm
Lurtotecan	Phase II	Glaxo/Gilead science
NK012 (nanoparticle formulation	Phase II	Nippon Kayaku
Oral topotecan (Hycamptin)	Phase III	GlaxoSmithKline
PG-Camptothecin	Phase II	Cell Therapeutics
Rubitecan (9-nitro camptothecin)	Phase III	SuperGen

1. 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

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. 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 (a 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.

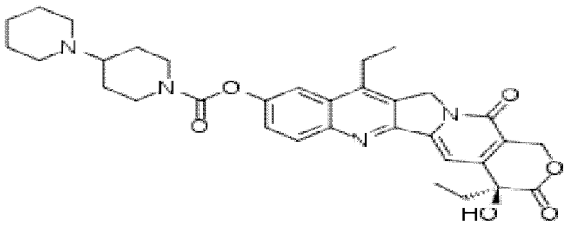
Topotecan Should not be used in patients who are pregnant or breast-feeding. Topotecan is contraindicated in patients who already have severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils <1 500 cells/mmand/or a platelet count of <100 000/mm. Topotecan is contraindicated in patients with severe renal impairment (creatinine clearance of <20 mL/min).

Combinations with topotecan in clinical trial:-

Combination	Use
genistein- topotecan	in prostate cancer cells
Topotecan and Cytarabine	in Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia
Nonplatinum Topotecan Combinations Versus Topotecan Alone	Recurrent Ovarian Cancer
Topotecan in Combination with Vincristine	for Treatment of Pediatric Solid Tumor Xenografts

2. Irinotecan-HCL

Irinotecan is an antineoplastic enzyme inhibitor primarily used in the treatment of colorectal cancer. It's brand name is Camptosar, CP0 , IRINOTECAN, CPT-11.



Irinotecan

Irinotecan inhibits the action of topoisomerase I. Irinotecan prevents religation of the DNA strand by binding to topoisomerase I-DNA complex. The formation of this ternary complex interferes with the moving replication fork, which induces replication arrest and lethal double-stranded breaks in DNA. As a result, DNA damage is not efficiently repaired and apoptosis (programmed cell death) occurs. Side effects include Gastrointestinal complications, such as nausea, vomiting, abdominal cramping, diarrhea, and infection.

Use for the treatment of metastatic colorectal cancer (first-line therapy when administered with 5-fluorouracil and leucovorin). Also used in combination with cisplatin for the treatment of extensive small cell lung cancer. Irinotecan is currently under investigation for the treatment of metastatic or recurrent cervical cancer.

Irinotecan Hydrochloride Trihydrate for Injection is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

Combinations with irinotecan in clinical trial

COMBINATION	USE	TRIAL PHASE
Oxaliplatin + Irinotecan	Gastrointestinal Tumors	Phase I Studies With Pharmacokinetics
Bevacizumab Alone and in Combination With Irinotecan	in Recurrent Glioblastoma	phase II,
irinotecan and cisplatin	in patients with metastatic neuroendocrine tumors	phase II trial
Irinotecan and Capecitabine	in Patients with Previously Treated Non-Small Cell Lung Cancer	Phase II
docetaxel– irinotecan	in advanced esophageal cancer	Phase II
Gemcitabine and Irinotecan	in patients with metastatic bladder cancer	phase II trial
Sorafenib and Irinotecan	in Pediatric Patients With Solid Tumors	Phase 1

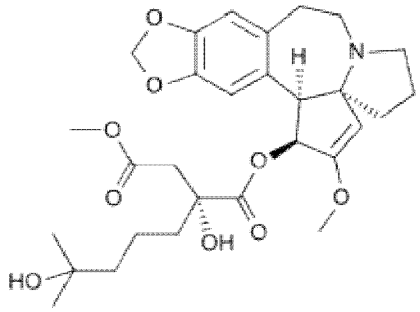
E. Cephalotaxanes

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

Cephalotaxus harringtonine

1. HOMOHARRINGTONINE:-

Omacetaxine mepesuccinate (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 ChemGenex and is on fast track approval schedule in the United States. Omacetaxine has been granted orphan drug status in the U.S. and in 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 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).

combinations with homoharringtonine in clinical trial

Combination	Use
homoharringtonine, Ara-C and idarubicin	treatment of newly diagnosed acute myeloid leukemia patients
Homoharringtonine in combination with cytarabine and aclarubicin (phase-2)	in patients with de novo acute myeloid leukemia
Homoharringtonine (HHT) in combination with interferon alpha	patients with newly diagnosed chronic myelogenous leukemia (CML)
homoharringtonine and low-dose cytosine arabinoside combined with G-CSF or GM-CSF	treat the relapsed or refractory acute myeloid leukemia (AML), geriatric AML and advanced myelodysplastic syndromes
Homoharringtonine + Imatinib Mesylate (phase-2)	Myeloid Leukemia
I.V. Administration of Homoharringtonine Combined with the Oral Administration of Gleevec (phase-2)	in the Treatment of Patients With CML in Chronic, Accelerated and Blast Phase

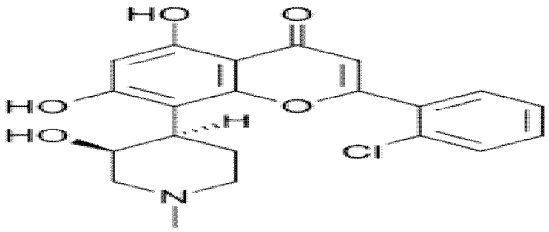
F. Flavones

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

1. Flavopiridol (Alvocidib)

Rohitukine (C16H19O5N), a chromane alkaloid, was first reported from Amoora rohituka (Roxb.) Wight & Arn. and then from Dysoxylum binectariferum Hook. f., both from the family Meliaceae. **Alvocidib** (also known as **Flavopiridol** or **HMR-1275**) is a cyclin-dependent kinase inhibitor under clinical development for the treatment of chronic lymphocytic leukemia. It has been studied also 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.

Dysoxylum binectariferum



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. Investigated for use/treatment in esophageal cancer, leukemia (lymphoid), lung cancer, liver cancer, and lymphoma (unspecified).

Combinations with alvocidib in clinical trial

Combination	Use	Trial phase
Trastuzumab and Flavopiridо	Breast Cancer	Phase 1
acetylsalicylic acid, alvocidib, clopidogrel bisulfate	Head and Neck Cancer Thromboembolism	Phase 2
Alvocidib (Flavopiridol), Ara-C and Mitoxantrone (FLAM)	Acute Myelogenous Leukemia	Phase 2
flavopiridol in combination with gemcitabine and irinotecan	in patients with metastatic cancer.	phase I
Flavopiridol in Combination With Paclitaxel	in Patients With Advanced Solid Tumors	Phase I
flavopiridol and docetaxel	in human LNCaP prostate cancer cells	–

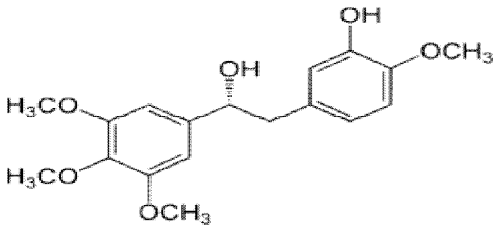
G. Stilbenes

Stilbenes used as multidrug resistance modulators and apoptosis inducers in human adenocarcinoma cells.

1. Combretastatin (Ave8062a)

The combretastatins are a class of natural stilbenoid natural phenols. A variety of different natural combretastatin molecules are present in the bark of Combretum caffrum, commonly known as South African Bush Willow.

Combretum caffrum,



Combretastatin

Combretastatin analogues in clinical trials:-

Name of analogue	Clinical status	Developer
AVE-8062 (AC-7700)	Phase I	Sanofi-Aventis
AVE-8064	Phase I	Sanofi-Aventis
AVE-8063	Phase I	Sanofi-Aventis
CA4PO4 (combrestatin A-4 phosphate	Phase II	OXiGENE

Members of the combretastatin family possess varying ability to cause vascular disruption in tumors. Combretastatin binds to the β-subunit of tubulin at what is called the colchicine site, referring to the previously discovered vascular disrupting agent colchicine. Inhibition of tubulin polymerization prevents cancer cells from producing microtubules.

Combretastatin A-4, the most potent naturally occurring combretastatin known, its phosphate prodrug (CA-4-P), and

other analogs of CA-4 such as ombrabulin are currently being investigated in a number of clinical trials. In July 2007 the pharmaceutical company OXiGENE initiated a 180-patient phase III clinical trial of CA-4-P in combination with carboplatin for the treatment of anaplastic thyroid cancer.[2] There is currently no fully FDA approved treatment for this form of cancer. The main side effect of combretastatin seems to be high blood pressure. In the ovarian cancer trial, this was controlled with medication. It also cause low blood counts and hair loss. combretastatin A-2 *contraindicated* for women of childbearing age.

Combinations with combretastatin in clinical trial

COMBINATION	USE	TRIAL PHASE
Combretastatin A4 Phosphate (CA4P) in Combination with Bevacizumab	in Patients with Advanced Cancer	Phase I
Oxegene, Combretastatin A4 Prodrug (CA4P)	solid tumor cancers	Phase Ib trial
CA-4-P in combination with carboplatin	treatment of anaplastic thyroid cancer	phase III

Recent Study

The structures of a number of active compounds isolated and characterized in our recent work on plant anti-cancer agents and progress on the bioactive constituents of nine of these plants is described in the following paragraphs.Three ent-kaurene diterpenoids have been isolated as cytotoxic constituents of the root bark of Parinari curatellifolia Benth. (Chrysobalanaceae), collected in Zimbabwe. These are the known compound, 15-oxozoapatlin , and the novel analogs, 13-methoxy-15-oxozoapatlin and 13- hydroxy-15-oxozoapatlin . These compounds were broadly cytotoxic when tested in the human tumor cell panel at the College of Pharmacy, University of Illinois (UIC), with the most potent cytotoxic activity being observed in each case in the A431 human epidermoid carcinoma cell line . Since it was obtained in reasonably large quantity, and because of its structural novelty and cytotoxic potency, compound 2 was subjected to a mechanistic investigation. It was found to react with the nucleophiles L-cysteine and b-mercaptoethanol, although it did not react with either DNA or guanosine. The effects of this compound were studied on the growth of human ZR-75-1 breast cancer cells, and it was determined that the biosynthesis of DNA, RNA, and protein was reduced in treated cells, and that accumulation at the G2/M phase of the cell cycle was seen. It was concluded that the cytotoxic activity of 13-methoxy-15-oxozoapatlin is mediated in part by means of a Michael-type addition with a sulfhydryl-containing protein or other cellular component, which results in the blockage of cell-cycle progression . Compound 2 was selected for testing in vivo against a KB human epidermoid cancer cell model, implanted subcutaneously, although it was not active at its maximum tolerated dose.

However, on the basis of successful preliminary evaluations in the National Cancer Institute 60-cell line tumor panel , and an in vivo hollow ®ber assay , 15-oxozoapatlin has been selected for future murine xenograft testing. From Aglaia elliptica Bl. (Meliaceae), a tropical rainforest tree obtained from Thailand, the known cyclopenta[b]benzofuran, methyl rocaglate and four novel analogs (5±8) were isolated and structurally characterized . Compound 8 was found to possess an unusual formyl ester substituent. All of these compounds exhibited potent and broad cytotoxicity against a panel of human cell lines, and compound 5 was selected for follow-up biological and mechanistic studies . After 24 or 32 h this substance induced accumulation at the G1/G0 phase of the cell cycle of cultured Lu1 human lung cancer cells, with normal cell-cycle dynamics observed subsequently at later time periods. During the course ofwash-out experiments, colony formation was not reduced, even though cell proliferation was observed in a normal manner. Compound 5 markedly reduced protein synthesis, although it had no effect on nucleic acid synthesis at a much higher concentration level. Accordingly, it was concluded that this compound acts as a cytostatic agent . In a preliminary study on the antitumor potential of 5 on athymic nude mice implanted subcutaneously with BC1 human breast cancer cells, tumor growth was inhibited by treatment with a dose of 10 mg/kg body weight administered intraperitoneally three times a week. This effect lasted for some 23 days, after which tumor growth paralleled that of a control group . Additional biological evaluation of compound 5 is presently being undertaken at the National Cancer Institute. From the Madagascan plant, Domohinea perrieri Leandri (Euphorbiaceae), four new bioactive compounds were isolated, represented by three phenanthrene derivatives

(9±11) as well as the hexahydrophenanthrene derivative, domohinone , whose structure and stereochemistry were con®rmed by single-crystal X-ray crystallography [24]. Of these compounds, only compounds 9 and 10 were signi®cantly cytotoxic against the human tumor cell panel. However, all four compounds were active in an assay designed to determine bleomycin-mediated DNA strand-scission activity , with compounds 9±11 being more potent in this regard than compound 12 . Compounds 9±12 were rated as representing 1.21, 1.08, 1.10, and 0.91 `bleomycin units', respectively, with 9±11 being about 800-fold less potent in the DNA strand-scission assay than bleomycin . Members of an unusual group of acylated oligorhamnosides were obtained as cytotoxic constituents of the stems of the Thai species Mezzetia leptopoda (Hook. f. & Thomas) Oliver (Annonaceae). The ®rst of these, compound 13, was obtained as a novel analog in the mezzetiaside series, and was assigned the trivial name mezzetiaside 8. This was obtained with three known compounds, mezzetiasides 2±4 (14±16), as well as additional analogs based on only two rhamnose units, whose structures are not shown. Compounds 13±16 were found to be weakly active as cytotoxic agents, and all showed some selectivity for the Col2 human colon cancer cell line (ED50 values of 4.3±8.2 mg/mL) . The stems of the Thai plant Vatica diospyroides Sym. (Dipterocarpaceae) afforded an interesting oligostilbenoid as a cytotoxic constituent. This compound, vatdiospyridol , was assigned as a resveratrol tetramer after extensive analysis of the COSY, HMQC and HMBC NMR spectra, of both the parent compound and a permethylated derivative, and the stereochemistry was postulated using a combination of NOESY NMR data interpretation and energy-minimized molecular modeling. Compound 17 was found to be signi®cantly cytotoxic against human oral epidermoid (KB), colon cancer (Col2), and breast cancer (BC1) cell lines, and is the ®rst resveratrol tetramer to be reported to exhibit cytotoxicity against cancer cells . It is of interest to note that in our investigation on V. diospyroides (E)-resveratrol 3-O-b-D-glucopyranoside was isolated, providing some circumstantial evidence that the tetrastilbenoids may have resveratrol monomeric biogenetic precursors. This is the initial report of a resveratrol monomer from the plant family Dipterocarpaceae, although resveratrol dimers, trimers, and tetramers were reported previously . Although in our screening program to date, relatively few alkaloids have been investigated, a new analog 18 of the potent cytotoxic agent, tubulosine was isolated and structurally characterized from the stems of Pogonopus speciosus (Jack). K. Schum. (Rubaceae), collected in Panama. (±)-Tubulosine , also present in the same sample, was extremely potent in our cell culture panel, with the best activity demonstrated against the Lu1 human lung cancer cell line (ED50 < 0.001 mg/mL) [29]. It has been known for some time that tubulosine is active in vivo, when tested in the L1210 murine leukemia test system . It is of interest that the novel compound (±)-10,20,30,40-tetradehydrotubulosine was less potent as a cytotoxic agent in the cell panel in which it was evaluated by about two orders of magnitude, when compared with tubulosine (19). Compound 18 could prove useful as a negative control in future biological experiments utilizing the potent cytotoxin tubulosine . While all other plants mentioned in the present section of the chapter were obtained in tropical rainforest areas, separate samples of the ¯owers and leaves of Ratibida columnifera (Nutt.) Wood & Standl. (Compositae) were collected in Texas. Work-up of these samples resulted in the isolation and characterization of two new xanthanolides and a new nerolidol sesquiterpene . In addition, three xanthanolides of previously known structure were isolated and identi®ed . Xanthanolides 20±24 demonstrated broad cytotoxic activity when evaluated against a panel of human cancer cell lines. The nerolidol derivative 25 showed only weak general cytotoxicity. Of the cytotoxic isolates, the known compound 23 [9a-hydroxy-seco-ratiferolide 5a-O-(2-methylbutyrate)] was selected for further biological evaluation. In a 25 cell-line tumor panel, representing a diverse group of mouse and human tumors, ®broblasts, and normal bovine endothelial cells, compound 23 was found to exhibit a mean IC50 value of 1.46 mM, and exhibited a novel selectivity pattern, when effects on ovarian cancer cells (p53 mutant A2780R, parental wild-type A2780S), colon cancer cells (MDR. HCT116/ VVM46, MDRÿ HCT 116), leukemic cells (HL-60, CCRF-CEM), and normal bovine aortic endothelial cells were examined . It was then decided to examine the biological properties of 9a-hydroxy-seco-ratiferolide 5a-O-(2-methylbutyrate) (23) in greater detail. This sesquiterpene lactone was investigated

for its effects on the cell cycle and on apoptosis, and was found to induce G1 arrest at a concentration level of 1.16 mg/mL, in wild-type p53 A2780S cells. In p53 mutant A2780R cells, S traverse time was reduced, in addition to G1 arrest. Both of these ovarian cancer lines underwent apoptosis when subjected to higher concentrations of 23, with the p53 wild-type cells being more sensitive than the p53 mutant cells. In the concentration range 10±100mM, compound 23 was found to have no effects on tubulin polymerization, on the inhibition of the catalytic ability of topoisomerase I and II enzymes, or on DNA intercalation. However, compound 23 was regarded as inactive when evaluated in vivo in two murine xenograft systems, namely, the M109 murine lung carcinoma and the HCT116 human coloncarcinoma models . Four bioactive ¯avonoids (26±29) were isolated from the combined leaves and stems of Uvaria hamiltonii Hook. f. et Th. (Annonaceae), collected in Thailand. The 5,7-dimethoxylated ¯avanones 26 and 27 were accorded the trivial names hamiltones A and B, respectively. Compounds 28 (hamiltrone), an aurone, and 29, a chalcone analog of 28, were also obtained in this investigation. All four compounds demonstrated strand-scission activity in the previously mentioned DNA strand-scission assay, with compound 28 being active at a dose of one-tenth of those of the other three compounds (activity of 26±29: 1.1, 1.0, 10.0 and 0.6 `bleomycin units', respectively) . A novel prenylated xanthone, tovobrevimastone , along with a known analog, manglexanthone , were isolated as cytotoxic constituents of the roots of Tovomita brevistaminea Engl. (Guttiferae), collected in Brazil. These compounds were evaluated as signi®cantly cytotoxic (EC50 < 5 mg/mL) for the KB (human oral epidermoid) cell line.

CONCLUSION

It is apparent that at present, drug-based therapeutic strategies will predominate in the 21st century. Thus, the discovery of new drugs effective against resistant tumors is an important and necessary strategy in improving chemotherapy. Natural drugs have found direct medical application as drug entities, but they also serve as chemical models or templates for the design, synthesis, and semisynthesis of novel substances, such as paclitaxel (Taxol), vincristine (Oncovin) and camptothecin, in the treatment of human cancer . Although there are some new approaches to drug discovery, such as a combination of chemistry and computer-based molecular modeling design, none of them can replace the important role of natural products in drug discovery and development.

REFERENCES

1. G Samuelson . Drugs of natural origin: a textbook of Pharmacognosy. 4th edition, Stockholm, Swedish Pharmaceutical Press, 1999.
2. GM Cragg; DJ Newmann; KM Snader. Journal of Natural Products, 1997, 60, 52-60.
3. LD Kappor. CRC Handbook of Ayurvedic medicinal plants. Boca Raton, Florida, CRC Press, 1990, 416-417.
4. GM Cragg; DJ Newmann. Journal of Ethnopharmacology, 2005, 100, 72-79
5. T Kutluk; A Kars. General Knowledge about cancer. Ankara; Turkey cancer investigation and fight society publications, 1998, 7-15.
6. S Turgay; D Sar. Turkistan, Premethod, 2005, 436-441.
7. R Pinar. To investigate knowledge of Turkish people about cancer. Cancer agenda, 1998, 2, 66-73.
8. JR Mann; N Dibois. Drug Discovery Today, 2004, 403-409.
9. JS Bertan. Molecular aspects Medicine, 2001, 21, 167-223.
10. Estrogen and cancer website, 2006.
11. BN Ames; LS Gold. The causes and prevention of cancer procedure natl. Academic sciences USA. 1995, 92, 5258-5265.
12. S Koduru; DS Grierson. Current Science, 2007, 92, 906-908.
13. American Cancer Society, Facts and Figures, 1999.
14. S Madhuri. Plant Archives, 2008, 8, 13-16.
15. S Sivalokanathan; M Ilayara. Indian Journal of Experimental Biology. 2005, 43, 264-67.
16. GM Crag; DJ Newmann. Journal of Ethnopharmacology, 2005, 100, 72-79.
17. GJ Creemer; G Bolis; G Scarfome; I Hudson. Topotecan, Journal of Clinical oncology, 1996, 14, 3056-3061.
18. JR Bertino. Oncology, 1997, 24, S18-S23.
19. AL Harvey. Trends Pharmaceutical Sciences, 1999, 20, 196-98.
20. H Itokawa; X Wang. Homoharringtonine and related compounds. In: Cragg GM, Kingston DGI. Newman D (eds) Anticancer agents from natural products. Boca Raton, Florida, Brunner- Routledge Psychology Press, Taylor and Francis Group. 2005, 47-70.
21. K Ohsumi; R Nakagawa; Y Fukuda; T Hatanaka. Journal of Medicinal Chemistry, 1998, 41, 705-06.
22. GR Petit; SB Singh; ML Niven; E Hamel. Journal of Natural Products, 1987, 50, 119-20.

23. RH Cichewitz; SA Kouzi. Medicinal Research Review, 2004, 24, 90-114.
24. E Pisha; H Chai; IS Less; JM Pezzuto. Natural Medicine, 1995, 1, 1046-51.
25. GM Cragg; DJ Newmann; S Holbeck. Curent Cancer drug targets, 2002, 2, 279-308.
26. L Pieters; T Debruyne; M Claeys. Journal of Natural Products, 1993, 56, 899-906.
27. JL Hartwell. Plants used against cancer; A survey. Lloyadia. 1969, 32, 158-176.
28. MI Lopes; J Lopes. Journal of Ethnopharmacology, 2004, 95, 437-445.
29. J Popoca; A Aguilar; D Alonso. Journal of Ethnopharmacology, 1998, 59,173-77.
30. T Howiriny; M Sohaibani. Journal of Ethnopharmacology, 2005, 98, 287-94.
31. A Calis; D Yuruker; AD Tasdemir. Planta Medica, 1997, 63, 183-86.
32. J Liu; H Shen. Cancer Letters, 2000, 153, 85-93.
33. B Fernanda; J Daniela. Toxicon, 2005, 45, 459-66.
34. S Lee; KT Lim. Journal of Food Sciences, 2003, 68, 466-470.
35. **HALL T. C.** : Chemotherapy of cancer.. New Eng. J. Med.. 266:289,1962;.
36. **FROST J. W., GOLDWEIN M. I., BRYAN J. A.** : Clinical experience with vincaleukoblastine in far-advanced Hodgkin's disease and various malignant states.. Ann. Intern. Med.. 58:584,1962;.
37. MIDWEST COOPERATIVE CHEMOTHERAPY GROUP, : Vinblastine in neoplastic disease.. Cancer Res.. 23:169,1963;.
38. **HODES M. E., ROHN R. J., BOND W. H., YARDLEY J. M., CARPENING W. S.** : Vincaleukoblastine. IV. A summary of two and one-half years' experience in use of vinblastine.. Cancer Chemother. Rep.. 16:401,1962;.
39. **KARNOFSKY D. A.** : Meaningful clinical classification of therapeutic responses to anti-cancer drugs. (editorial).Clin. Pharmacol. Ther.. 2:709,1961;.
40. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. JAMA. 1985;253:1590-1591.
41. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. 1987. Available from Louis P. Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
42. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia. 1983;1:426-428.
43. M. C. Wani, D. M. Brown, M. J. O'Neill, J. A. Lewis, J. M. Besterman. In New Trends in Natural Product Chemistry (Atta-ur-Rahman, M. I. Choudhary, eds), pp. 79±94. Harwood Academic Publishers, Amsterdam (1998).
44. A. Artuso. Drugs of Natural Origin. Economic and Policy Aspects of Discovery, Development, and Marketing, pp. 3±4. The Pharmaceutical Products Press. Binghampton, New York (1997).
45. Anonymous. Taxotere.com for Healthcare Professionals: Pharmacokinetics. Sanofi-aventis U.S. LLC.

-

