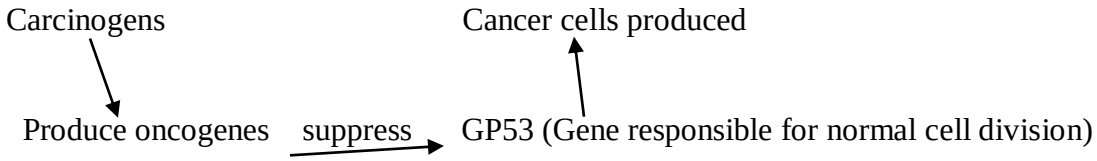
Tumor Inhibitors from Plants

Introduction

Cancer is a generalized term applied to a series of malignant diseases which may affect many different parts of body. These diseases are characterized by a rapid and uncontrolled formation of abnormal cells which may mask together to form a growth called Tumor. Tumor may be benign or malignant.

Mechanism of Cancer

Abnormal genes are called oncogenes. Whenever, any carcinogen enters the body there is production of oncogenes which suppress the GP53, a gene responsible for controlled and coordinated cell division, hence there would be growth of cancerous cells.



Causes of Tumor

- Genetic factor
- Carcinogens e.g. tobacco smoking (due to nitropepridine agent)
- Certain type of viruses
- Radiations
- Alcohol
- Pollution
- Diet

Types of Tumors

Carcinoma

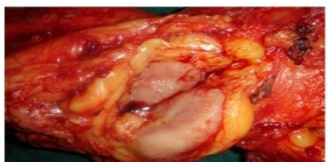
It occurs 90%. It is the malignant tumor of epithelial cells.
e.g. (Lung, liver, renal cell carcinoma).

Sarcoma

It occurs 5%. It is the malignant tumor of flesh (soft) tissues like cartilages, bones. e.g. osteosarcoma.

Lymphoma

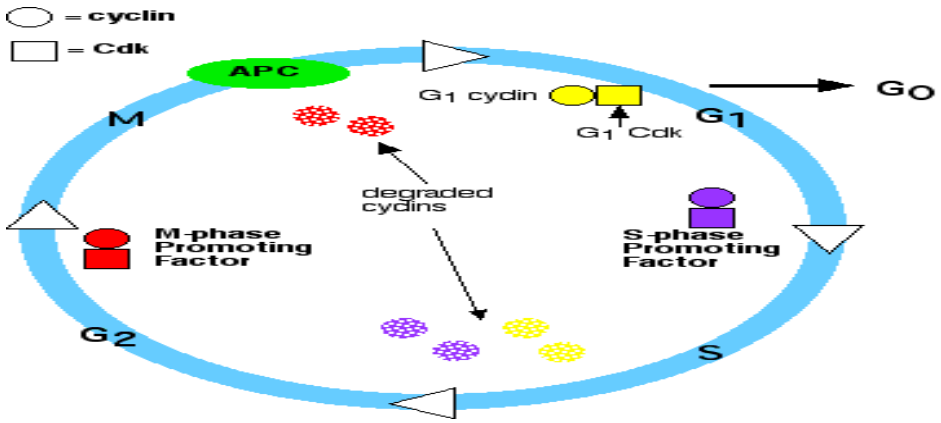
It occurs 2.5%. It is the disorder of lymphoid tissues, solid tumor.
E.g. non-Hodgkin's and Hodgkin lymphoma.



Leukemia

It occurs 2.5%.
It is the malignant disease of blood forming organs, characterized by proliferation and development of leucocytes.

Cell Cycle:



- **G_1 = growth and preparation of the chromosomes for replication**
- **S = synthesis of DNA and duplication of the centrosomes**
- **G_2 = preparation for mitosis**
- **M = mitosis**

PLANTS CONTAINING ANTI TUMOR DRUGS

Plant materials have been used in treatment of malignant diseases or to inhibit the growth of tumor for centuries. Following are the plants which are commonly used as tumor inhibitors.

Catharanthus (Vinca)

Botanical Origin: *Catharanthus roseus* or *Vinca roseus*
Family Name: Apocyanaceae
Common Name: Periwinkle
Part Used: Dried whole plant

Introduction

Traditionally this plant has been used as anti-diabetic but has not been scientifically confirmed. The credit for the discovery of anti-tumor activity goes to Canadian workers who discover during their work in 1955-1960 that the extract of leave produce leukopenic effect in rats.

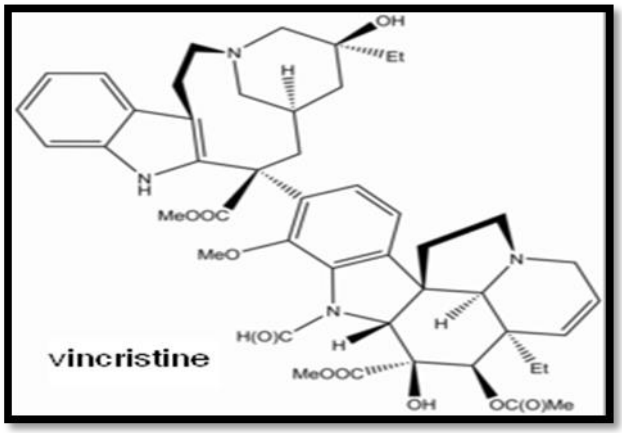
Extraction and Isolation of Constituents

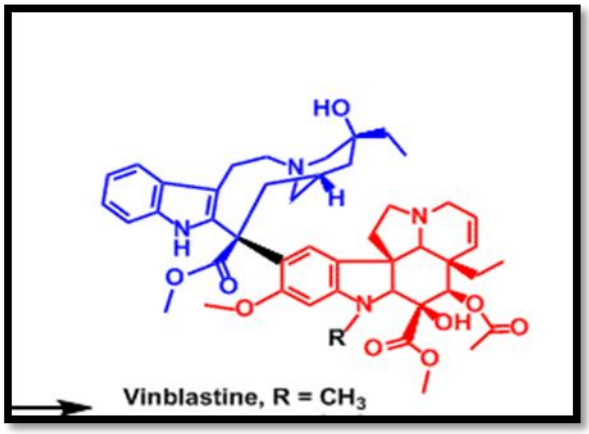
Based on solubility patterns – First, fractionation (alcoholic or aqueous extract is treated with various solvents in increasing order of polarity) is done. Then column chromatography is carried out with alumina as adsorbent or solid phase.

Composition

About 150 alkaloids have been isolated from the plant. 30 indole alkaloids have been isolated e.g.Vincristine, Vinblastine and Ajmalicine. Other alkaloids seen are Ajmalicine, Lochnaine, Tetrahydroalstonine and Serpentine. Around 500 kg of the crude drug is required for extraction of 1 g of Vincristine (concentration in 0.002% per plant). Therefore, extraction is very costly.

Vincristine and vinbalstine are commercially available alkaloids for cancer chemotherapy. They are present in minute quantity.





Mechanism of action

They are M-phase specific (Mitosis phase) and block mitosis in metaphase. They bind to micro-tubular protein, tubulin that form the mitotic spindle during cell division. In this way, these drugs block the ability of tubulin to polymerize so no cell division occurs and cell death takes place.

Uses

❖ **Vincristine**

- Used in treatment of acute lymphocytic leukemia in children
- Wilms' tumor/nephroblastoma (tumor of nephron)
- Hodgkin and non-hodgkin lymphoma (tumor of lymph nodes)
- Also used in lung cancer

Dose

1 – 30 µg /kg by body weight I/V

❖ **Vinblastine**

- It is administered with bleomycin and cisplatin (synthetic drugs) for treatment of testicular carcinoma (tumor of testis)
- Also used in Hodgkin and non-hodgkin lymphoma
- In breast cancer

Dose

100 µg / kg body weight I/V

Podophyllum

Botanical Origin: *Podophyllum peltatum* or *Podophyllum emodi*

The use of this drug as anti-cancer is started in 1948.

Family Name: Berberidaceae

Common Name: May apple root, Wild Mandrake.

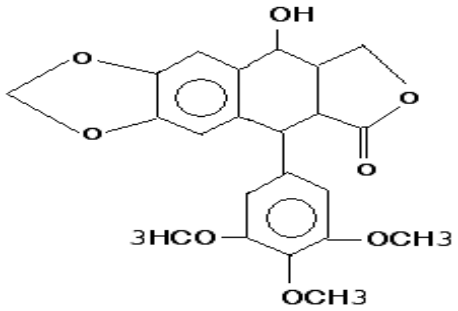
Part Used: Rhizomes, Roots, Fruits.

Habitat: A perennial herb common in moist shady situations in the

eastern parts of Canada & USA. The drug is collected in Virginia, Kentucky, Carolina and Indiana.

Composition

Main active constituent is podophyllotoxin which is a resin. It is prepared by pouring an alcoholic extract of the drug into water and collecting and drying the precipitate. American Podophyllum yields 2-8% podophylotoxin. These compounds possess cytotoxic or antitumor activity, but activity is loss on mild base treatment.



Podophylotoxin

Mechanism of Action

They are S-phase specific. They form complex with enzyme topoisomerase II which results in single strand breakage of DNA and thus cell death occurs.

Uses

Etoposide, Teniposide are semi-synthetic products of podophyllotoxin and are used in treatment of lung cancer, testicular cancer, ovarian cell cancer, leukemia. Also used in brain tumor in children.

Taxol (Paclitaxel)

Botanical Origin: *Taxus brevifolia*

Part used: Taxol is obtained from bark of mature plant which is about 100 years old

Family Name: Taxaceae

Common Name: Pacific Yew.

Part Used: Bark of mature plant.

Habitat: Taxus brevifolia (Pacific Yew or Western Yew) is a conifer native to the Pacific Northwest of North America. It ranges from southernmost Alaska south to central California, mostly in the Pacific Coast Ranges, but with an isolated disjunct population in southeast British Columbia and south to central Idaho.

Production:

Almost all paclitaxel produced was derived from bark from the Pacific yew, the harvesting of which kills the tree in the process.

All paclitaxel production uses plant cell fermentation (PCF) technology .This starts from a specific taxus cell line propagated in aqueous medium in large fermentation tanks. Paclitaxel is then extracted directly, purified by chromatography and isolated by crystallization.

Composition

The plant contain different diterpenoid derivative called Taxenes. Taxol concentration is much lower than that of other taxene derivative e.g. Baccatin III is up to 0.2% as compared to 0.02% of taxol. Commercially taxol is obtained by semi-synthesis of baccitin III. Substitution of side chain of taxol has resulted in Docetaxel which is more potent than taxol and has fewer side effects.

Mechanism of Action

It binds to tubulin and promotes polymerization and stabilization of polymer instead of disassembly thus stable micro-tubules are formed which are non-functional and results in cell death.

Uses

It is used in treatment of ovarian cancer, breast and lung cancer. It is also used in the treatment of Kaposi's sarcoma.

Side Effects

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 2–3 days, changes in the color of the nails and tingling in the hands or toes. Dexamethasone is given prior to beginning paclitaxel treatment to mitigate some of the side effects.

Other Natural Anti-Tumor compounds from Plants

- ✓ Indicine-N-oxide from *Heliotropium indicum* showed no evidence of hepatotoxicity, possessed significant antitumor activity and underwent clinical trials. The compound showed substantial activity in acute leukemia.
- ✓ The cucurbitacins from *Marah oreganus* is the most cytotoxic compound known but its narrow index makes the compound unpromising as therapeutic agents.
- ✓ Colchicine from *Colchicum autumnale* is used as mitotic poison in plant breeding and its anti-tumor activity are closely related.
- ✓ Colchicine derivates e.g. Demecolcine are being used in cancer treatment in some countries.
- ✓ The anti-tumor activity of Acronycine, an Acridone alkaloid isolated from *Achronychia baueri* exhibited a very broad anti-tumor spectrum.