

ANTICANCER DRUGS FROM PLANT ORIGIN

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Cancer is a general term applied to a series of malignant diseases that may affect different parts of body. That is characterized by rapid and uncontrolled growth of abnormal cells forming a tumour generally. If the process is not destroyed it leads to death of the individual. Cancer is commonly seen in all higher animals and plants also develop growths that resemble cancer.

The anticancer drugs either destroy neoplastic cells or modify their growth. The treatment of cancer is different because generally there are few physiological and biochemical differences between normal and cancerous cells. If a drug inhibits a cancerous cell, normal cell is also affected. But the cancerous cells have some specific characters viz., they grow and divide rapidly compared to normal cells. But other cells of the body which grow and divide rapidly are also affected.

Broadly the anticancer drugs can be classified into three groups:

- 1. Alkylating agents.**
- 2. Antimetabolites.**
- 3. Natural products.**

The Alkylating agents include

- Nitrogen mustards (Cyclophosphamide, Chlorambucil)
- Nitrosoureas (Carmustine, Lomustine)
- Alkyl sulfonates (Busulfan) and
- Thiazines (Dacarbazine)

The treatment of cancer was started in 1940 when nitrogen mustard was used. The alkylating agents produce highly reactive carbonium ion intermediates, which transfer alkyl groups to cellular macromolecules by forming covalent bonds. Ultimately there occurs abnormal cross-linking or abnormal base pairing or scission of DNA strands.

Antimetabolites resemble the normal cellular metabolites or component of DNA or coenzymes involved in nucleic acid synthesis. They competitively inhibit utilization of normal substrates or get themselves incorporated forming dysfunctional macromolecules.

These antimetabolites are

- Folic acid antagonists (Methotrexate)
- Purine antagonists (Mercaptopurine) and
- Pyrimidine antagonists (5-fluorouracil).

The third major group is Natural Products. It includes the drugs obtained from the plants, animals, microbes etc. most of the natural drugs used now a days are obtained from plants like vinca alkaloids, Taxanes, epipodophyllotoxins (semisynthetic derivatives). The antibiotics used in chemotherapy are obtained from microorganisms eg (Actinomycin D, Doxorubicin, Danorubicin etc).

Hormones are also used in cancer chemotherapy eg; Estrogen like Fosfestrol, antiestrogens like Tamoxifen, antiandrogens like Flutamide and 5- α reductase inhibitor like Finasteride.

Role of Plants in Cancer Treatment

Plant materials have been used in the treatment of malignant diseases for centuries. The ancient Chinese used *Podophyllum* over 2000 years ago as an antitumour drug. Resins from the root of plant *Podophyllum hexandrum* and related American species, the May-apple (*P.peltatum*) have yielded a number of lignans and their glycosides having antitumour activity. The major constituent from these two species- podophyllotoxin and peltatins are not used systematically but the semi synthetic derivatives of podophyllotoxin i.e. etoposide and teniposide have given good results in clinical trials. Etoposide is been used for small-cell lung cancer and testicular cancer. Teniposide is used in pediatric cancers.

It is revealed that in ancient times (about 180 AD) the juice obtained from woody nightshade *Solanum dulcamara* has been used to treat cancers, tumours and warts. There are a number of references available, about its use in literature of many countries. The active antitumour compound has been identified as steroidal alkaloid glycoside β -solamarine.

The alkaloids of *Catharanthus roseus* are very much used in cancer chemotherapy. Research in this plant was stimulated by its mention in folklore, not as a cure for cancer but the treatment of diabetes. But when its activity was tested, no hypoglycemic activity was detected, instead the treated test animals became susceptible to bacterial infections, and this lead the researchers to undertake extensive examination for possible immune suppressive principles causing these effects. A number of bisindole alkaloids, having anticancer activity have been isolated from this plant, most common are- vinca leukoblastine and leurocristine (vincristine). These compounds are used alone or in combination with other forms of therapy for cancer treatment. Vincristine is clinically more important than vinblastine and is especially used in the treatment of childhood leukemia.

How a plant source extract become a drug

An intensive survey is done to identify and collect plants with suspected antitumour activity and the collected samples/plants were tested for their cytotoxic, antitumorous and anticancer activity.

A cytotoxic agent is toxic to tumour cells in vitro and if this toxicity occurs to tumour cells in vivo the agent is named as antitumorous. The term anticancer is reserved for materials that are toxic to tumour cells in clinical trials as per United States National Cancer Institute guidelines for investigation methods. In the more recent systematic studies, every portion of the plant and every fraction of the extract is tested biologically before any constituent is isolated and characterized. Usually only those fractions, showing biological activities are studied further. It is well known fact that isolated constituents of plant drugs may not give the same clinical response, as a crude preparation of that plant drug. It may be due to the reason that the total therapeutic activity of plant extract is greater or different from the therapeutic activities of the of the individual plant extract. Synergism or antagonism between different parts may occur, leading to this effect.

The extracts, which prove their antitumour activity, are tested for their in vivo anticancer activity. The extracts showing the positive response become candidates for fractionation studies leading to isolation and purification of the active principles.

Promising chemicals are subsequently tested against a range of standard experimental neoplasms, and then considered for preclinical toxicological studies if these results are sufficiently encouraging.

Main Natural Products Used as Tumour Inhibitors

Class	Compound	Plant Sources
Monoterpine	Allamandin	<i>Allamanda cathartica</i>
	4-Ipomeanol	<i>Ipomea batatas</i>
Diterpine	Jatrophone	<i>Jatropha gossypifolia</i>
	Taxodione	<i>Taxodium distichium</i>
	Taxol	<i>Taxus brevifolia</i>
Lignan	α and β -Peltatin	<i>Podophyllum peltatum</i>
	Podophyllotoxin	<i>P.hexandrum</i> <i>P.peltatin</i>
Isoquinoline	Emetine	<i>Cephaelis acuminata</i>
Bis-indole	Leurosine	<i>Catharanthus lanceus</i> & <i>C.roseus</i>
	Vinblastine	<i>C.roseus</i>
	Vincristine	<i>C.roseus</i>
Non-heterocyclic peptide	Colchicine	<i>Colchicine Speciosum</i>

Other natural products include *Tylocrebine*, a phnanthroindolizidine alkaloid obtained from *Tylophora crebiflora*. This alkaloid has adverse effects on CNS, so it was dropped from the trial studies. Chinese tree *Camptotheca acuminata*, showed broad spectrum of activity but it has also highly toxic effects.

Another plant *Brucea antidysenterica* is used in Ethiopia for the treatment of cancer. Systemic fractionation of this plant has lead to the isolation of *bruceantin*. This has shown high antileukemic activity at low doses. It acts by inhibition of protein synthesis, and it has also undergone clinical trials in man.

Several other natural products have also proved their anticancer activity to justify clinical trials or toxicological testing. The *diterpenes*, *triptolide* and *triptodiolide* isolated from *Tripterygium wilfordii* are potent antileukemic agents. The plant is not readily accessible and contains only small amounts of these agents.

Diterpenoid taxol (Paclitaxel) is another important plant derived anticancer agent with encouraging responses in different types of cancers. It is isolated from the bark of the pacific yew, *Taxus bravifolia*. Clinical trials have demonstrated its activity against ovarian and breast cancers, and taxol has become an important anticancer drug.

Taxol content of *Taxus bravifolia* is relatively low (0.01-0.03 %) and the bark from about 3 trees is required to produce one gram. This restricts availability of taxol for drug use and future supplies are nit assured.

Modes of Action

Most of the anticancer plant drugs used in chemotherapy inhibit the nucleic acid synthesis, but the mechanism of action differs widely. Some compounds are mitotic inhibitors eg. colchicines, podophyllotoxin, vincristine and maytansine. These drugs act by binding to the protein tubulin in the

mitotic spindles, preventing polymerization and assembly into microtubules. As during mitosis the chromosomes separate with the assistance of these microtubules, and after cell division, the microtubules are transformed back to tubulin.

Taxol, on the other hand, is completely different type of antimetabolic agent as it promotes the assembly of microtubules and stabilizes them against depolarization.

Podophyllin is a tubulin binder but its semisynthetic anticancer drug etoposide and teniposide have different modes of action. These drugs inhibit DNA synthesis and replication * enzyme topoisomerase II. Camptothecin on the other hand is known to have specific inhibitor of topoisomerase I system. Topoisomerase enzymes are involved in cutting and resealing of DNA strands.

A large number of natural tumour inhibitors act as alkylating agents like bruceantin, trptolide and elephantopin. Most agents are cytotoxic, killing normal and cancerous cell alike.

Plant Profile

CATHARANTHUS ROSEUS

The Madagascan periwinkle is also known as *Vinca rosea* and *Lochnera rosea*. It is indigenous to Madagascar but is now widely distributed throughout warm regions and much cultivated as an ornamental commercial supplies of the drug are obtained from both wild and cultivated plants produced in various locations including Africa, India, Thailand, Spain, USA and Australia.

The plant is 40-80 centimeter high and is woody at the base. About 150 alkaloids have been isolated from *C.roseus* e.g. ajmalicine, serpentine etc. 20 bisindole alkaloids having antineoplastic activity like vincristine, vinblastine have been derived from the plant.

PODOPHYLLUM AND PODOPHYLLUM RESIN

Podophyllum is also known as wild Mandrake. It is perennial herb, commonly present in moist shady situations in the eastern parts of Canada and USA. The rhizome is a meter in length, is dug up, cut into pieces about 10 cm in length and dried. The drug obtained was previously used as a vermifuge and emetic but now it is used as an anticancer drug, after a series of developments in drug.

INDIAN PODOPHYLLUM

Consists of dried rhizome and roots of the herb *Podophyllum hexandrum* found in Tibet, Afghanistan and the Himalayan areas of Pakistan and India. The drug is collected in India, Pakistan and china.

TAXUS BRAVIFOLIA AND TAXOL

The Pacific yew i.e. *Taxus bravifolia* is a slow growing shrub/tree found in forests of north west Canada and USA. The plant requires 100 years to get mature and to be large enough for exploitation of its bark. At this age plant becomes 6-9 meter high and its trunk about 25 cm in diameter. The wood of plant is not suitable, only bark is removed from it during the period of May-August. Although taxol is currently extracted from the dried barks it is realized that it cannot provide long term supply of drug. One gram of drug is obtained from 3 plants and a patient require 2 gram of taxol for a course of treatment.

