Anticancer therapy new Approach: An overview

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Abstract: Cancer is a major public health burden in both developed and developing countries. Now a days many treatments are find out by many researcher to inhibit cancer disease. In which plant – derives compound have been an important source of several clinically useful anticancer agents including taxol, vinblastine, the camptothacin derivatives, topotecan and etoposide derived from epipodophyllotoxin are in clinical use over the world. About 30 plant derives compounds have been isolated so far and are currently under clinical trial. Also The Present review abridges synthetic route to some food and drug administration-approved anticancer drugs. This review also contain idea about how to microtubules used in therapy of cancer.

Key words: Introduction and history of cancer, Plant based drug, Synthetic route containing drug, Microtubules.

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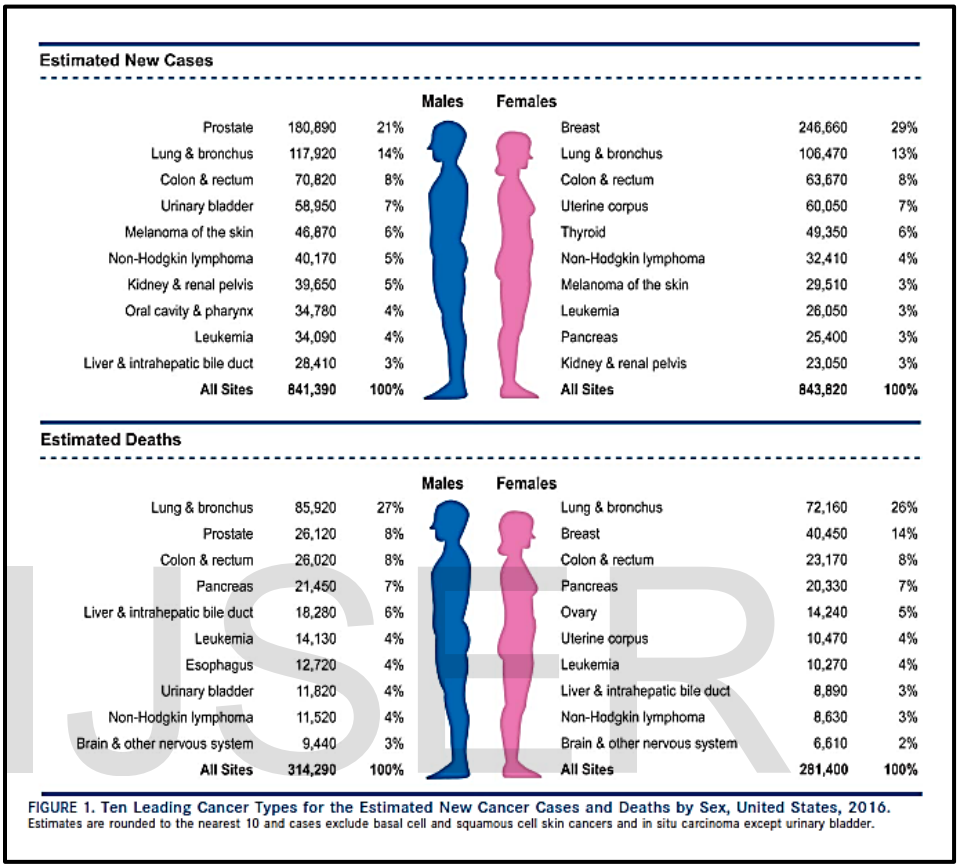
1. INTRODUCTION

Cancer

The study of cancer - called oncology, is the work of countless doctors and scientist around the world whose revelation in anatomy, physiology, chemistry, epidemiology. The origin of the word cancer is credited to the Greek physician Hippocrates, Who is considered the “Father of Medicine”. Hippocrates used the terms carcinons and carcinomas to describe non-ulcer forming and ulcer-forming tumour.[1]

Cancer is a 2nd leading cause of death in developed countries. In, 2016, 1,685,210 new cancer cases, and 595,690 cancer deaths are projected to occur in United States. Cancer statistics, in 2016 are shown in figure[2]



Estimated New Cases

Males			Females		
Prostate	180,890	21%	Breast	246,660	29%
Lung & bronchus	117,920	14%	Lung & bronchus	106,470	13%
Colon & rectum	70,820	8%	Colon & rectum	63,670	8%
Urinary bladder	58,950	7%	Uterine corpus	60,050	7%
Melanoma of the skin	46,870	6%	Thyroid	49,350	6%
Non-Hodgkin lymphoma	40,170	5%	Non-Hodgkin lymphoma	32,410	4%
Kidney & renal pelvis	39,650	5%	Melanoma of the skin	29,510	3%
Oral cavity & pharynx	34,780	4%	Leukemia	26,050	3%
Leukemia	34,090	4%	Pancreas	25,400	3%
Liver & intrahepatic bile duct	28,410	3%	Kidney & renal pelvis	23,050	3%
All Sites	**841,390**	**100%**	**All Sites**	**843,820**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	85,920	27%	Lung & bronchus	72,160	26%
Prostate	26,120	8%	Breast	40,450	14%
Colon & rectum	26,020	8%	Colon & rectum	23,170	8%
Pancreas	21,450	7%	Pancreas	20,330	7%
Liver & intrahepatic bile duct	18,280	6%	Ovary	14,240	5%
Leukemia	14,130	4%	Uterine corpus	10,470	4%
Esophagus	12,720	4%	Leukemia	10,270	4%
Urinary bladder	11,820	4%	Liver & intrahepatic bile duct	8,890	3%
Non-Hodgkin lymphoma	11,520	4%	Non-Hodgkin lymphoma	8,630	3%
Brain & other nervous system	9,440	3%	Brain & other nervous system	6,610	2%
All Sites	**314,290**	**100%**	**All Sites**	**281,400**	**100%**

FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2016.
Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Fig.1. Cancer statistics

During the 1970s, scientists discovered 2 particularly important families of genes related to cancer; Oncogenes and tumor suppressor genes.[1]

- **Oncogenes** These genes cause cell to grow out of control and formation of cancer cells.
- **Tumor suppressor genes** These are normal genes that slow down cell division, repair DNA errors, and tell cell when to die, When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer.

Cancer may be defined as a disease in which abnormal cells divide uncontrollably and destroy body tissue. Cancer is malignant growth known as neoplasm which is related to the

automous growth of tissues and uncontrolled growth of cells, with loss of differentiation and with metastasis, and spread to other tissues and organs form the origin.[3]

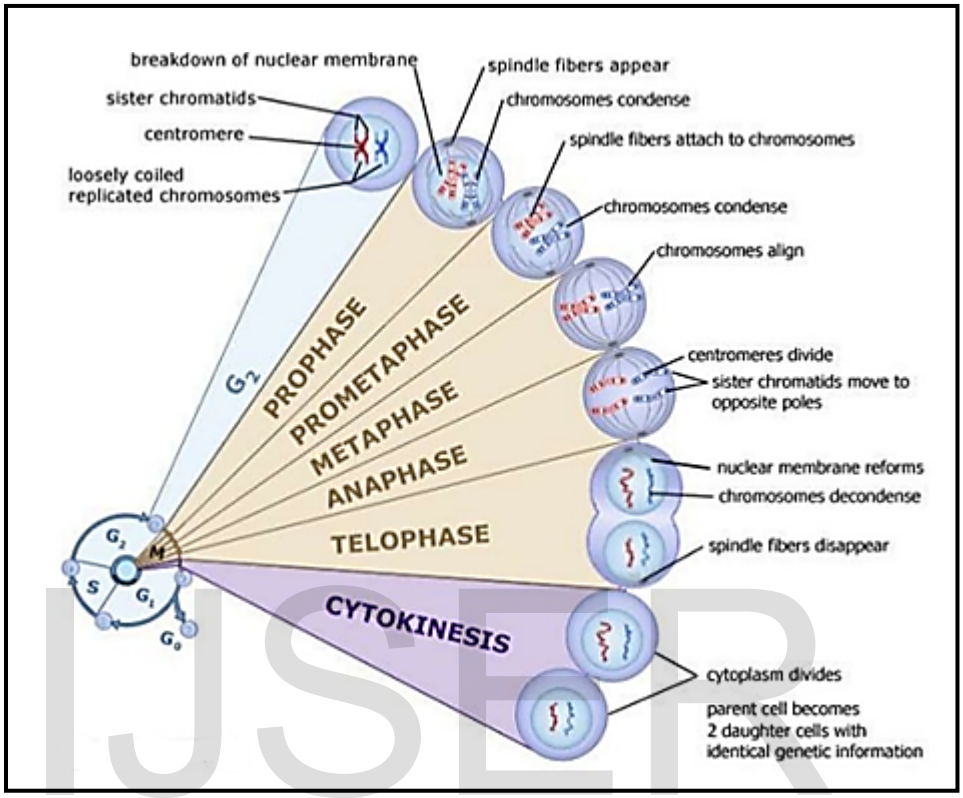


Fig.2. Cell Cycle

Cell division is a process in which cell passes its genes onto the two daughter cells, each cell is clone or extract of itself. Sometimes, this process proceeds wrong and the genes in a cell may suffer a variation or some problem may occur in DNA replication during cell division.

Cancer or Neoplasm is the appearance of tumor. A tumor is an abnormal mass of a tissue; the growth of tumor is uncoordinated and persists even after the cessation of the stimulus which provokes the change. A tumors may grow any site in the body.

1.1 Tumors are of two kinds.

1.1.1. Benign tumors (Non-malignant tumors)

1.1.2 Cancerous tumors (malignant tumors)

1.1.1 Benign tumors (Non-malignant tumors)

The benign tumors grow slowly in size. They remain confined to the place of origin in body part and do not spread to other part of the body. Growth of tumors may responsible for crowding to other organs of body and result in pain. Benign tumors may become malignant tumors. The benign tumors are easily discovered and remove.

1.1.2 Cancerous tumors (malignant tumors)

The cancerous tumors grow slowly in beginning. The symptoms do not appear at this stage. This type of tumor has the ability to multiply uncontrollably, to spread to various parts of body and invade surrounding neighboring tissue like roots of a tree and form secondary tumors and so on. These tumors responsible for death of person by increasing interference with body's life processes.

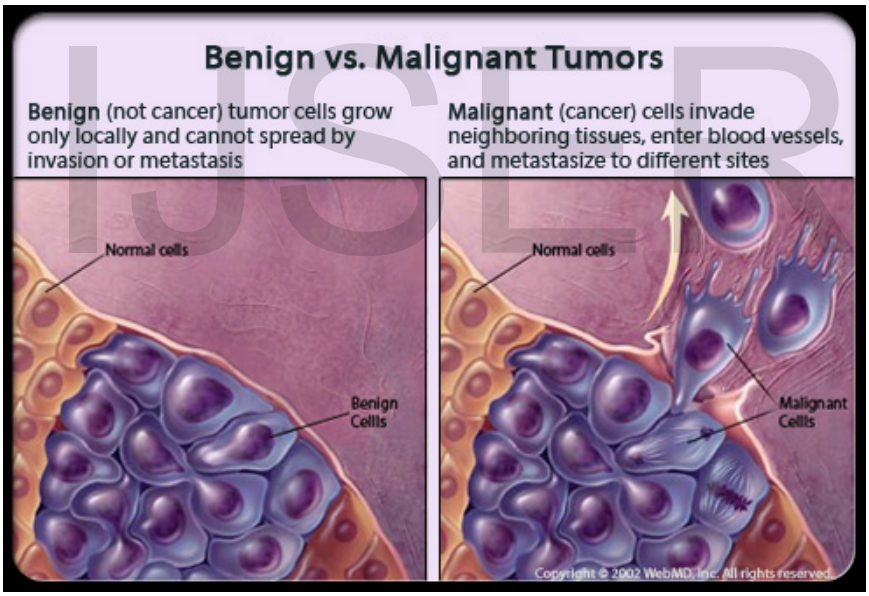


Fig.3. Types of Tumor[4]

1.1.2 Sign and symptoms of cancer

1. A sore that does not heal.
2. Change in bowel or bladder habits.
3. Cough and hoarseness.
4. Unexpected weight loss.

5. Loss of appetite.
6. Low grade fever persist.
7. A hard tissue (lump) which grows larger, changes its size.
8. Unusual bleeding or discharge.
9. Indigestion or difficulty swallowing
10. Excessive loss of blood during menstruation period in women.

1.1.3 Causes of cancer

Cancer is not a hereditary or contagious. The factors are known which favour cancer, these are called carcinogens. It is impossible to prove that what caused a cancer in any individual, because most cancers have multiple causes.

Cancer is one type of disease that is infectious can be caught by being near a person who has it, mainly it can be caused by oncoviruses and cancer bacteria.[4]

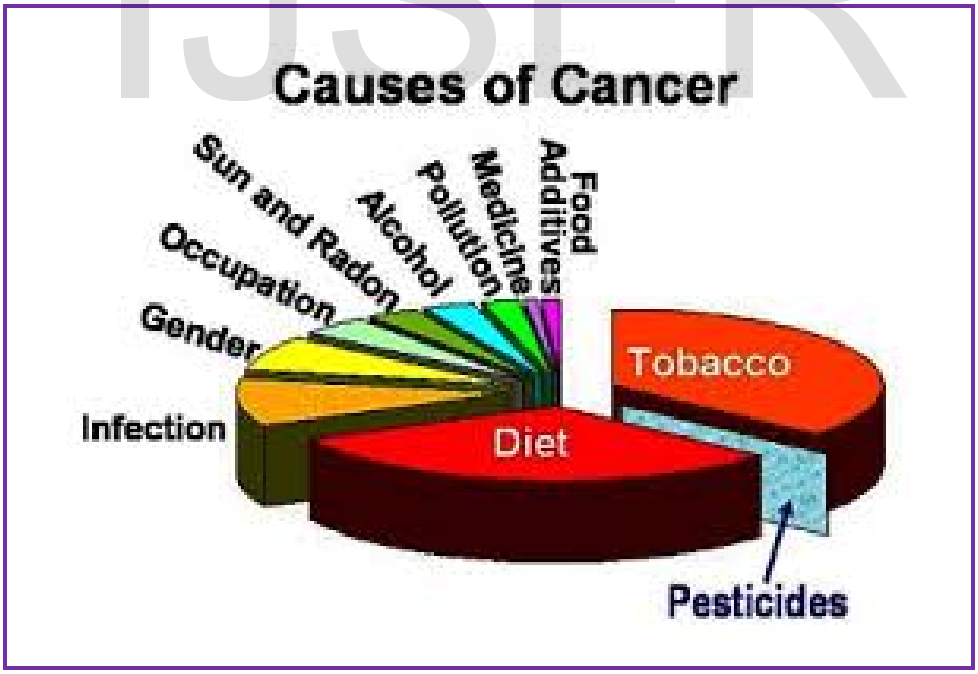


Fig.4.Causes of Cancer[4]

1.1.3.1 Chemicals

Several chemicals are responsible for cancer. example nicotine, caffeine, pesticides, asbestos, nickel, dyes, artificial sweeteners. Drinking alcohol, Benzene, Dioxane, CCl_4, Clofibrate, Aniline can also increase the risk of developing of cancer.

1.1.3.2 Radiations

Radiation also causes cancer. X-rays, ionizing radiation, nonionizing ultraviolet radiation, Gamma radiation, and Nuclear fission that are carcinogenic. Radiation energy causes chromosome breakage, translocations and point mutations, where ionizing radiation activates Rash oncogenes and inactivates the Rb tumor suppressor gene. Free radicals are developed in tissues by X-rays and gamma rays, resultant hydroxide, superoxide interacts leading to molecular damage and contributing carcinogenic effect.

Natural UV radiations from the sun can cause skin cancer.

1.1.3.3 Smoking

Tobacco smoking is associated with many types of cancer, and causes 90% of lung cancer. Daily long-term vamping with a high voltage (5.0 V) electronic cigarette may form formaldehyde-forming chemicals at a greater level than smoking, which was determined to be a lifetime cancer risk of approximately 5 to 15 times greater than smoking.

1.1.3.4 Tobacco chewing

Tobacco in various forms of usage can cause cancer of lungs, larynx, mouth, pharynx, oesophagus, bladder, pancreas and probably kidney.

1.1.3.5 Diet and exercises

Diet, physical inactivity, and obesity are related to approximately 30–35% of cancer deaths. More than half of the effect from diet is due to over nutrition rather than from eating too little healthy foods. Diets that are low in vegetables, fruits and whole grains, and high in processed or red meats are linked with a number of cancers.

1.1.3.6 Hormones

Hormones are responsible for development of cancer by promoting cell proliferation. Insulin-like growth factors and their binding proteins play a key role in cancer cell proliferation, differentiation and apoptosis, suggesting possible involvement in carcinogenesis. Hormons are important agents in sex related cancer like a ovary, testis, and also thyroid and bone cancer.

1.1.3.7 Viruses

Oncogenic viruses contain either DNA or RNA as their genome. ‘polyoma virus’ and ’SV 40’ viruses play important role in producing cancer. Small in size and their circular genomes code for about 5-6 proteins. Appropriate cells being infected with these viruses and results in malignant transformation. Virus infection is risk of cervical cancer, liver cancer. Bacterial infection may also increase the risk of cancer.

1.1.3.8 Physical agent

Some substances causes cancer primarily their physical rather than chemical, effects on cells. Example of this is prolonged exposure to asbestos, naturally occurring mineral fibres which are cause of mesothelioma.

1.1.3.9 Foods

Many foods are responsible for causing cancer, they all are enlist as below;

- Genetically Modified Foods
- Microwave Popcorn
- Canned goods
- Grilled Red Meat
- Refined Sugar
- Salted, Pickled, and Smoked foods
- Soda and Carbonated Beverages
- White Flour

1.1.4 Types of Cancer

Type of cancer	Affected area
Breast	Lungs, Liver, Bones
Colon	Liver, Lungs
Kidney	Lungs, Liver, Bones
Lung	Adrenal gland, Lungs
Melanoma	Skin, Muscle, Liver
Ovary	Peritoneum, Liver
Pancreas	Liver, Lungs
Prostate	Bones, Lungs, Liver
Rectum	Liver, Adrenal gland
Stomach	Lungs, Liver, Bones
Thyroid	Lung, Bones

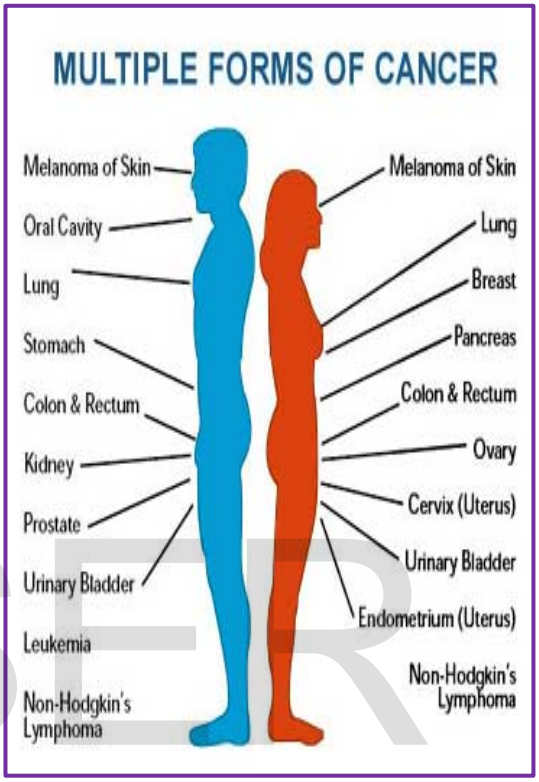


Table 1. Types of Cancer

Fig.5. Types of Cancer[4]

2. Treatment of Cancer

There are many cancer treatment are available in the world. The types of treatments will depend on the type of cancers. Some people with cancer will have only one treatment. But most people have a combination of treatments for single cancer, such as surgery with chemotherapy, immunotherapy, targeted therapy, radiation therapy and hormone therapy.

Chemotherapy is the use of any to treat any disease. But some people, the word chemotherapy means drug used for cancer treatment. It is often shortened to “chemo”. Surgery and radiation therapy remove, kill or damage cancer cells in a certain area, but Chemo can work throughout the whole body. When used with other treatments, Chemotherapy can; Make a tumour cells in to

the smaller size before surgery or radiation therapy. Destroy cancer cells that may remain after treatment surgery or radiation therapy.[5]

In present review, We discuss main three treatment of cancer and they are following as :

(1) Plant based derived drug treatment.
(2) Synthetic route containing drug treatment.
(3) Microtubules.

2.1 Plant derived Anticancer drug in clinical development[6]

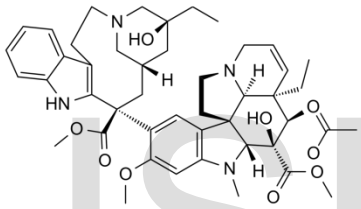
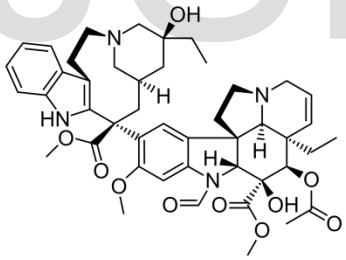
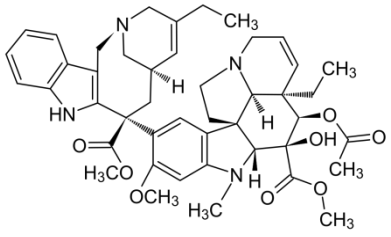
Vinca alkaloid,
Etoposide,
Teniposide,
Taxans,
Camptothacins,

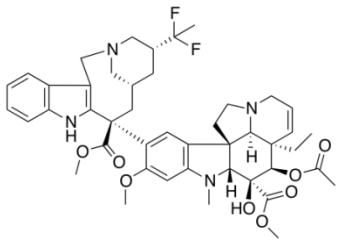
A. Vinca Alkaloid:

The mechanism of action of vinca alkaloid is that they inhibit the cell proliferation by affecting the microtubular dynamics during mitosis, and this causes a block during mitosis leading to apotosis. Vinca alkaloid include, Vinbalstin and Vincristine, Vinorebline and Vindesine are obtained from the Catharanthus roseus (Apocyanaceae).

Catharanthus roseus

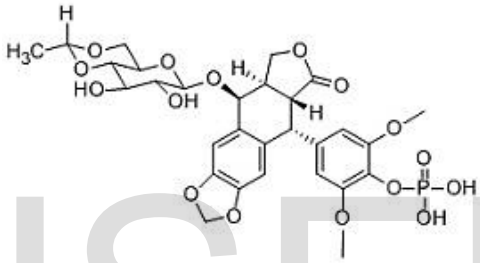
Vinca alkaloid analogue in clinical trial

Binding Domain	Releted drug / anlouge	Therapeutic uses	Stages of clinical development
Vinca Alkaloid	**Vinblastin** 	Hodgkin's disease, Testicular germ cell cancer	In clinical use; 22 combination trials in progress
	Vincristine 	Leukaemia, Lymphoma	In Clinical use; 108 combination trail in progress
	Vinorevline 	Solid tumors, Lymphomas, Lung cancer	In clinical use; 29 phase I-III clinical trials in progress
	Vinflunine	Blader, non small cell lung cancer, breast	Phase III

		cancer	

Etoposide:

Etoposide phosohate is an anticancer agents, Which belong to the drug type topoisomerase inhibitor.

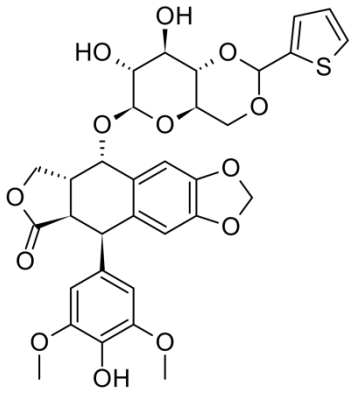


Etoposide phosphate

Etoposide forms a ternary complex with DNA and the topoisomerase II enzyme, prevent re-ligation of the DNA strands, and by doing so causes DNA strands to breack.

Teniposides:

A Semisynthestic derivatives of podophyllotoxins that exhibit anticancer activity. Teniposide inhibits DNA synthesis by forming a complex with topoisomerase II and DNA. This complex induces breaks in double strands DNA and prevents repair by topoisomerase II binding.



Teniposide

Taxanes :

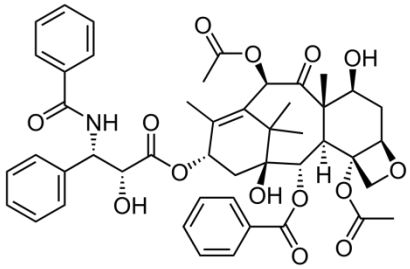
The Prototype taxans is the natural product paclitaxel, originally known as taxol and first derived from the bark of the pacific yew tree. Docetaxel is semisynthetic analogue of paclitaxel. Taxanes enhance stability of microtubules, preventing the separation of chromosome during anaphase.

Bark of Pacific yew

1. **Paclitaxel**

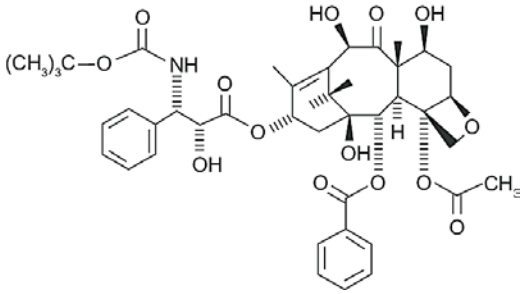
   A cyclodecane isoloated from the bark of the pacific yew tree, taxus bevifolia. It stabilized microtubules in their polymerized from leading to cell death. Abraxane is

the latest attempt to improve upon paclitaxel, one of the leading chemotherapy treatment. It's brand name is Abraxane, Abraxis, Bioscience, Epotaxol, Onxol, Paxceed, Paxene, Taxol.



Paclitaxel

2. **Docetaxel :** Docetaxel is a clinically well-established anti mitotic chemotherapy medication. The cytotoxic activity of docetexel is exerted by promoting and stabilizing microtubule assembly, while preventing physiological microtubule disassembly in absence of GTP. The main use of docetaxel is the treatment of a variety of cancer after the failure of anthracycline-based chemotherapy.[7] Marketing of docetaxel as Taxotere is mainly towards the treatment of brest, prostate and other non small cell cancer.[8]



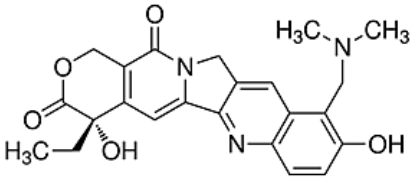
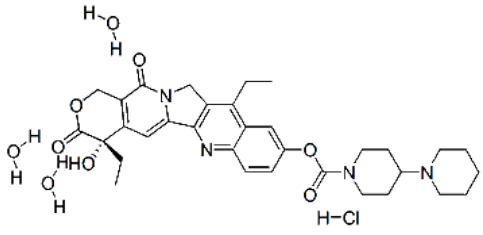
Docetaxel

Camptothecins:

It is a cytotoxic quinolone alkaloid which inhibit the DNA enzyme topoisomerase I. It was discovered in 1966. It was isolated form the bark and stem of Comptotheca acuminate, a tree native China used as a cancer treatment.

Comptotheca acuminate

Camptothecins containing drugs:

Camptothecins Drug	**Topotecan** 	It is a topoisomerase inhibitor. Topotacan has the same mechanism of action as irinotecan and is belived to exert its cytotoxic effects during the S-phase of DNA Synthesis
	Irinotecan-HCL 	It inhibit the action of topoisomerase I.

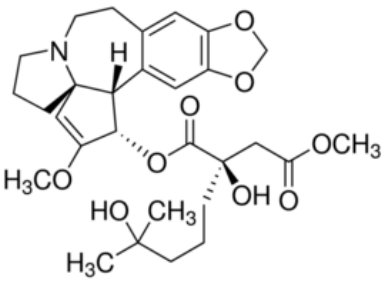
Cephalotaxanes

Cephalotaxus sources of harringtonine, it is a promising new anti cancer alkaloid.

Cephalotaxus harringtone

1. **Homoharringtonine:**

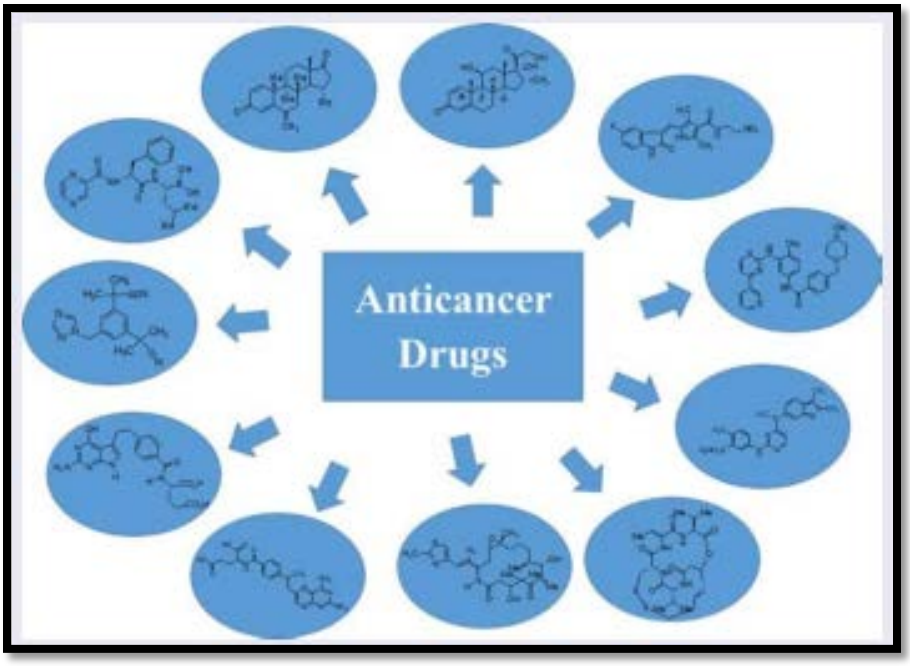
   Omacetaxine mepesuccinate is an alkaloid from Cephalotaxus harringtone that is investigated for potential use as a drug against hematological cancers.

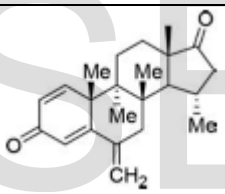
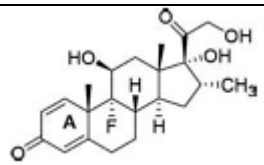
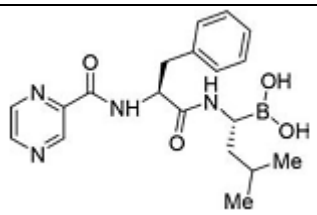
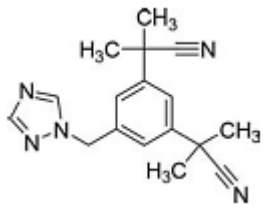


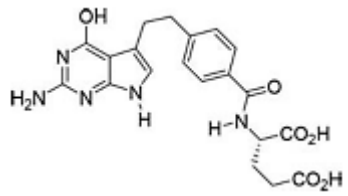
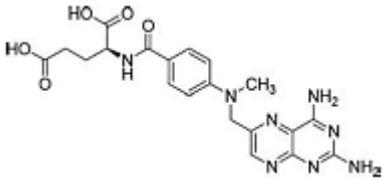
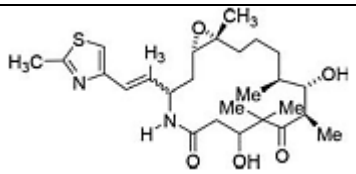
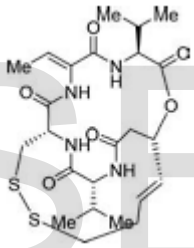
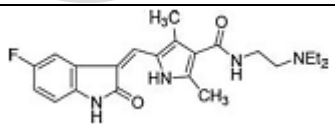
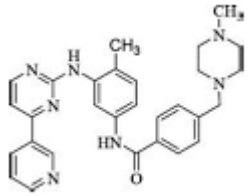
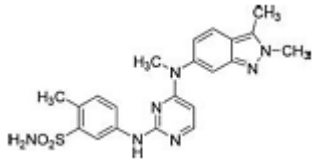
Homoharringtonine

(2) Synthetic route containing drug treatment[9] :

This review abstracts information available from many literature sources to provide a selection of the some of the commonly used synthetic routes for food and drug administration approved drugs.



Sr. No.	Drug	Structure	Activity
1	**Exemestane**		To treat Breast Cancer
2	**Dexamethasone**		To treat metastatic brain tumors
3	**Bortezomib**		To treat meloma and mantile cell lymphoma
4	**Anastrozole**		To treat Breast Cancer

5	**Pemetrexed**		To treat pleural and non small lung cancer.
6	**Methotrexate**		To treat breast, head, neck, leukemia and bladder cancer.
7	**BMS247550**		To treat refractory metastatic and advanced breast cancer
8	**Romidepsin**		To treat T cell lymphoma.
9	**Sunitinib**		To treat renal cell GIT cancer.
10	**Imatinib**		To treat Chronic myeloid and GIT cancer.
11	**Pazopanib**		To treat renal cell carcinoma and soft tissue sarcoma.

(3) Microtubules used in Cancer therapy[8].

Highly dynamic mitotic spindle microtubules are among the most successful target for anticancer therapy. Microtubules-key component of the cycloskeleton-are long, filamentous, tube-shaped protein polymers that are essential in all eukaryotic cells. They are crucial in the development and maintenance of cell shape, in the transport vesicles, mitochondria and other components throughout cells, in cell signaling, and in cell division and mitosis. They are crucial in the development and maintenance of cell shape, in the transport of vesicles, mitochondria and other components throughout cells, in cell signalling, and in cell division and mitosis. Microtubules are composed of a -tubulin and ß -tubulin heterodimers (of dimensions 4 nm × 5 nm × 8 nm and 100,000 daltons in mass) arranged in the form of slender filamentous tubes that can be many micrometres lon see in FIGS 6. They are highly dynamic polymers and their polymerization dynamics are tightly regulated both spatially and temporally. The functional diversity of microtubules is achieved in several ways: through the binding of various regulatory proteins, including microtubule associated proteins (MAPs), to soluble tubulin and to the microtubule surfaces and ends; by expression of different tubulin isotypes, which have different functions; and through several post-translational modifications of tubulin. For example, human tubulin isotypes (6 forms of a -tubulin and 7 forms of ß –tubulin) are expressed at varying levels in different cells and tissues. These tubulins can be further modified post-translationally by polyglutamylation, polyglycylation, phosphorylation, acetylation, detyrosination/tyrosination and removal of the penultimate glutamic-acid residue of a –tubulins .There are many different MAPs, including the dynein and kinesin motor proteins, as well as many microtubule-regulatory proteins, such as survivin, stathmin, TOG, MCAK, MAP4, EB1, dynactinRAC1 and FHIT.[16-17] Microtubules are extremely important in the process of mitosis, during which the duplicated chromosomes of a cell are separated in to two identical sets before cleavage of the cell in to two daughter cells. Their importance in mitosis and cell division makes microtubules an important target for anticancer drugs.

Microtubules and their polymerization dynamics

The polymerization of microtubules occurs by a nucleation elongation mechanism in which the relatively slow formation of a short microtubules nucleus is followed by rapid elongation of the microtubule at its ends by the reversible, non covalent addition of tubulin dimers. It is important to emphasize that use energy provided by the hydrolysis of GTP at the time that tubulin with

bound GTP adds to the micro tubule ends; these dynamic later, the correct movements of the chromosomes and their proper segregation to daughter cells require extremely rapid dynamics, making mitosis exquisitely sensitive to microtubule targeted drugs. The biological functions of microtubules in all cells are determined and regulated in large part by their polymerization dynamics.[12-13] Microtubules show two kinds of non-equilibrium dynamics, both with purified microtubule systems *in vitro* and in cells. One kind of dynamic behavior that is highly prominent in cells, called 'dynamic instability', is a process in which the individual microtubule ends switch between phases of growth and shortening.[15] The two ends of a microtubule are not equivalent; one end, called the plus end, grows and shortens more rapidly and more extensively than the other (the minus end). The changes in length with time at the ends of a group of microtubules due to dynamic instability are illustrated in FIG. The microtubules undergo relatively long periods of slow lengthening, brief periods of rapid shortening and periods of attenuated dynamics or pause, when the microtubules neither grow nor shorten detectably. Dynamic instability is characterized by four main variables: the rate of microtubule growth; the rate of shortening; the frequency of transition from the growth or paused state to shortening (this transition is called a 'catastrophe'); and the frequency of transition from shortening to growth or pause (called a 'rescue'). Periods of pause are defined operationally, when any changes in microtubule length that might be occurring are below the resolution of the light microscope. The variable called 'dynamicity' is highly useful to describe the overall visually detectable rate of exchange of tubulin dimers with microtubule ends.

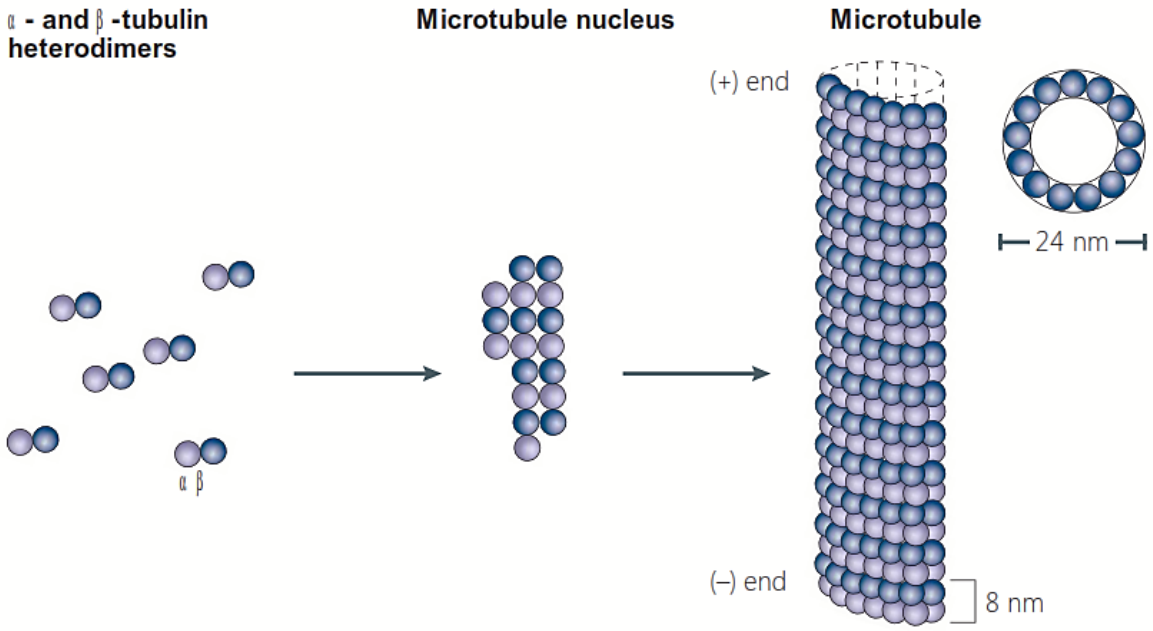


Fig. 6 Polymerization of microtubules

In this figure describe polymerization of tubules. In which heterodimers α and β tubulin assemble to form a short microtubule nucleus. Nucleation is followed by elongation of the microtubules at both ends to form a cylinder that is composed of tubulin heterodimers arranged head to tail in 13 proto filaments. Each microtubule has a so called plus end, with β tubulin facting the solvents, and minus end, with α tubulin facing the solvent.

Antibiotic drugs, their diverse binding sites on tubulin and their stages of clinical development

Binding Doamin	Related drugs or analouges	Therapeutic uses
Vinca Domain	Vinblastin (Velban)	Hodgin' disease. Testicular germ cell cancer
	Vincristine (Oncovin)	Leukamia, Lymphoma
	Vinorelbine (Navelbin)	Solid tumor, Lymphomas,

		Lung cancer
	Vinflunine	Bladder, Non small cell lung cancer, breast cancer
	Cryptophycin	Solid tumor
Colchicine domain	Colchicine	Non neoplastic disease
	Methoxybenzene sulphonamide	Solid tumor
Taxane site	Paclitaxel	Ovarine, breast and lung cancer
	Docetaxel	Prostate, brain, and lung cancer

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 tumor is an important and necessary strategy in improving chemotherapy. In these review both natural products and microtubule containing drugs are new approach for treatment of cancer. such 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.

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