



A REVIEW ON PLANT ORIGIN ANTICANCER DRUGS

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ABSTRACT

Globally cancer is a disease which severely effects the human population. There is a constant demand for new therapies to treat and prevent this life-threatening disease. Scientific and research interest is drawing its attention towards naturally-derived compounds as they are considered to have less toxic side effects compared to current treatments such as chemotherapy. The Plant Kingdom produces naturally occurring secondary metabolites which are being investigated for their anticancer activities leading to the development of new clinical drugs. In the present review, an attempt has been made to study the plants that have been used in the treatment of cancer.

KEYWORDS: Cancer, Causes, Types, Anticancer drugs, Mechanism, Herbal plants.

INTRODUCTION

Cancer is a leading cause of mortality, and it strikes more than one-third of the world's population and it's the cause of more than 20% of all deaths. Among the causes for cancer are tobacco, viral infection, chemicals, radiation, environmental factors, and dietary factors.^[1]

Cancer has been a constant battle globally with a lot of development in cures and preventative therapies. The disease is characterised by cells in the human body continually multiplying with the inability to be controlled or stopped. Consequently, forming tumours of malignant cells with the potential to be metastatic.^[2] Current treatments include chemotherapy, radiotherapy and chemically derived drugs. Treatments such as chemotherapy can put patients under a lot of strain and further damage their health. Therefore, there is a focus on using alternative treatments and therapies against cancer.^[3] For many years herbal medicines have been used and are still used in developing countries as the primary source of medical treatment. Plants have been used in medicine for their natural antiseptic properties. Thus, research has developed into investigating the potential properties and uses of terrestrial plants extracts for the preparation of potential nanomaterial based drugs for diseases including cancer.^[4] This article aims to take an overview of current plant derived compounds that have anticancer therapeutic properties and their developments in the field.

Cancer

Cancer is the uncontrolled growth of abnormal cells anywhere in a body. These abnormal cells are termed

cancer cells, Malignant cells, or tumor cells. These cells can infiltrate normal body tissues. cancer cells can break away from original mass of cells, travel through the blood and lymph systems, and lodge in other organs where they can again repeat the uncontrolled growth cycle. This process of cancer cells leaving an area and growing in another body area is termed metastatic spread or metastasis. For example, if breast cancer cells spread to a bone, it means that the individual has metastatic breast cancer to bone. This is not the same as "bone cancer," which would mean the cancer had started in the bone.

The following table (National Cancer Institute 2016) gives the estimated numbers of new cases and deaths for each common cancer type:

Cancer Type	Estimated New Cases	Estimated Death
Bladder	76,960	16,390
Breast (Female -- Male)	246,660 -- 2,600	40,450 -- 440
Colon and Rectal (Combined)	134,490	49,190
Endometrial	60,050	10,470
Kidney (Renal Cell and Renal Pelvis) Cancer	62,700	14,240
Leukemia (All Types)	60,140	24,400
Lung (Including Bronchus)	224,390	158,080
Melanoma	76,380	10,130
Non-Hodgkin Lymphoma	72,580	20,150
Pancreatic	53,070	41,780
Prostate	180,890	26,120
Thyroid	64,300	1,980

The incidence of cancer and cancer types are influenced by many factors such as age, gender, race, local environmental factors, diet, and genetics. Consequently, the incidence of cancer and cancer types vary depending on these variable factors. For example, the World Health Organization (WHO) provides the following general information about cancer worldwide:

- Cancer is a leading cause of death worldwide. It accounted for 8.2 million deaths (around 22% of all deaths not related to communicable diseases; most recent data from WHO).
- Lung, stomach, liver, colon, and breast cancer cause the most cancer deaths each year.
- Deaths from cancer worldwide are projected to continue rising, with an estimated 13.1 million deaths in 2030 (about a 70% increase)^[5]

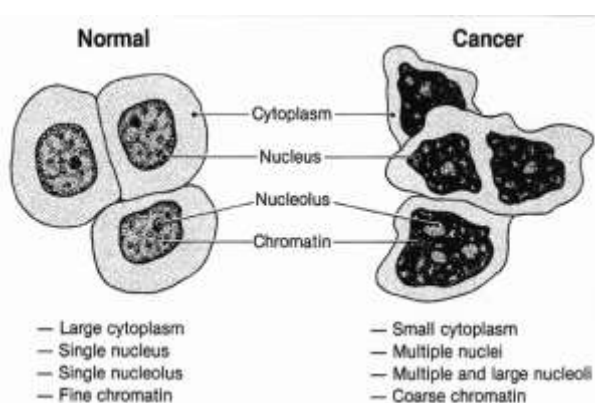


Figure 1: Normal cell and cancer cell structure.

Causes of Cancer

1. Exposure to carcinogenic agents or excessive radiation

Chemicals or radiation that produce cancer known as carcinogens. These carcinogens induced mutation. These are associated with 60 to 90% of cancer cases.

Eg. UV radiation in sunlight, Radioactive elements like Uranium, Radium, Thorium etc.

2. Heridity factor

This includes chromosomal abnormality enzyme immune defence system and hormonal imbalance. For eg. Susceptibility to lung cancer is associated with inducible level of Arylhydrocarbon hydroxylase.

3. Cultural factor

Include diet, smoking and drinking habits.

4. Occupational factors

Like ionizing radiation, chemical etc.

For eg. Coal tar, Mustard gas, chromium, Nickel, Asbestos can cause trigour lung cancer in employer working in chemical insulation and gas factories.

5. Viral origin (onco virus)

Human papillio virus (HPV) - Cause survehicle virus in human. Virus produces proteins that causes destruction of P53 genes (Tumour suppressor Gene). In case of abnormal P53 cell proliferate without control.

Types of Cancer

According to National Cancer Institute (NCI) classification, different types of cancer are classified as follows:

1. Carcinoma – epithelial origin
2. Sarcoma- Muscles or collective tissue origin
3. Leukemia - Rapid growth of abnormal leucocytes or WBC.
4. Glioma - Neural origin
5. Melanomas- Cancerous growth of Melanocytes.
6. Lymphoma - Lymphatic origin
7. Most commonly acquired cancers
 - a. Prostate cancer
 - b. Breast cancer
 - c. Lung cancer
 - d. Colon cancer
 - e. Rectal cancer

Cell Cycle and Cancer

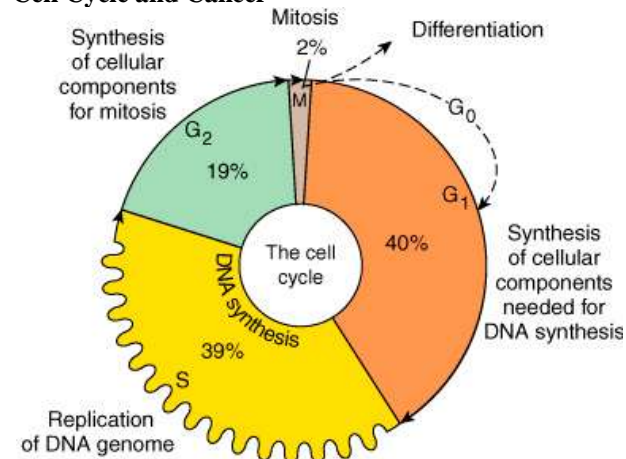


Figure 2: The cell cycle and Cancer: both Normal and Cancer cells must traverse before and after cell division.

Classification of Anticancer Drugs

1. **Alkylating Agents:** Cyclophosphamide, Melphelan, Nitrosourea,
2. **Platinum analogs:** Cisplatin, Carboplatin
3. **Antimetabolites:** Cytarabine, Fludarabine, Methotrexate
4. **Plant alkaloids:** Camptothecins, Etoposide, Paclitaxel, Vinblastine
5. **Antitumor antibiotics:** Bleomycin, Doxorubicin, Mitomycin
6. **Hormonal Agents:** Flutamide, Leuprolide, Tamoxifen,
7. **Differential Inducer:** Arsenic trioxide, Retinoic acid derivatives
8. **Gene targeted drugs:** Cetuximab, Dasatinib, Gefitinib, Imatinib

- 9. Immunomodulators:** including cytokines and growth factors
- 10. Antiangiogenesis drugs:** sorafenib, sunitinib, pazopanib.^[6]

Mechanism of Action of Anticancer Drugs

Chemotherapy drugs, are sometimes feared because of a patient's concern about toxic effects. Their role is to slow and hopefully halt the growth and spread of a cancer. There are three goals associated with the use of the most commonly-used anticancer agents.

1. Damage the DNA of the affected cancer cells.
2. Inhibit the synthesis of new DNA strands to stop the cell from replicating, because the replication of the cell is what allows the tumor to grow.
3. Stop mitosis or the actual splitting of the original cell into two new cells. Stopping mitosis stops cell division (replication) of the cancer and may ultimately halt the progression of the cancer.

Categories of Chemotherapeutic Drugs

In general, chemotherapy agents can be divided into three main categories based on their mechanism of action.

1. Stop the synthesis of pre DNA molecule building blocks

These agents work in a number of different ways. DNA building blocks are folic acid, heterocyclic bases, and nucleotides, which are made naturally within cells. All of these agents work to block some step in the formation of nucleotides or deoxyribonucleotides (necessary for making DNA). When these steps are blocked, the nucleotides, which are the building blocks of DNA and RNA, can not be synthesized. Thus the cells cannot replicate because they can not make DNA without the nucleotides. Examples of drugs in this class include methotrexate, fluorouracil, hydroxyurea, and mercaptopurine.

2. Directly damage the DNA in the nucleus of the cell

These agents chemically damage DNA and RNA. They disrupt replication of the DNA and either totally halt replication or cause the manufacture of nonsense DNA or RNA (i.e. the new DNA or RNA does not code for anything useful). Examples of drugs in this class include cisplatin, antibiotics - daunorubicin, doxorubicin, and etoposide.

3. Effect the synthesis or breakdown of the mitotic spindles

Mitotic spindles serve as molecular railroads with "North and South Poles" in the cell when a cell starts to divide itself into two new cells. These spindles are very important because they help to split the newly copied DNA such that a copy goes to each of the two new cells during cell division. These drugs disrupt the formation of these spindles and therefore interrupt cell division. Examples of drugs in this class of mitotic disrupters include: Vinblastine, Vincristine and Paclitaxel.

Herbal Medicine in Cancer Treatment

India is the largest producer of medicinal plants and is rightly called the "Botanical garden of the World". The medicinal plants, besides having natural therapeutic values against various diseases, also provide high quality of food and raw materials for livelihood. Considerable works have been done on these plants to treat cancer, and some plant products have been marketed as anticancer drugs, based on the traditional uses and scientific reports. These plants may promote host resistance against infection by re-stabilizing body equilibrium and conditioning the body tissues. Several reports describe that the anticancer activity of medicinal plants is due to the presence of antioxidants in them. In fact, the medicinal plants are easily available, cheaper and possess no toxicity as compared to the modern (allopathic) drugs. Medicinal plants have been used for thousands of years in folk medicines in Asian and African populations and many plants are consumed for their health benefits in developed nations. According to the World Health Organisation (WHO) some nations still rely on plant-based treatment as their main source of medicine and developing nations are utilising the benefits of naturally sourced compounds for therapeutic purposes.^[7]

Some important plants and its drugs to cure Cancer are listed below as:

1. *Camptotheca Acuminata* (Camptothecaceae)

It is 20m tall deciduous trees commonly known as Happy Tree or Cancer Tree. Camptothecin a natural alkaloid extracted from the bark of the tree. While Topotecan a derivative of Camptothecin and a type of Chemotherapeutic drug. Topotecan is the first topoisomerase-1 inhibitor for Ovarian cancer, Cervical cancer, Small cell lung cancer.^[8]

2. *Catharanthus Roseus* (Apocynaceae)

It is 1m tall evergreen shrub commonly known as Vincarosea. Vinblastine is a Vinka Alkaloid and a chemical analog of Vincristine and generated in Plant by joining of two alkaloids Catharanthin and Vindoline. It is an anti microtubule drug used to treat certain kinds of cancer, including Hodgkin's lymphoma, non-small cell lung cancer, breast cancer, Head and Neck cancer and Testicular cancer. It is also used to treat Langerhans cell histiocytosis.^[9]

3. *Podophyllum Hexandrum* (Berberidaceae)

It is 11-12 inches high from field commonly known as Himalaya mayapple. Podophyllotoxin is a non-alkaloid toxin lignin extracted from the roots and rhizomes of *Podophyllum* species. Podophyllotoxin and its derivatives display a wide selection in medicinal applications such as purgative, vesicant, anti rheumatic, antiviral, and antitumor agents. These derivatives include etoposide, teniposide and etophos. Their anticancer activity are under study and used in various chemotherapies, including lung cancer, lymphomas, and genital tumors.^[10]

4. *Annonama Crocarpa* (Annonaceae)

It is small evergreen tree commonly known as Graviola. Graviola produces a natural compound acetogenesis used as anti cancerous agent. According to the Purdue University, 1997 acetogenesis is effective in killing tumors and also resistant to anti-cancer agents and later in 2003 Taiwan researchers also stated that annonacin is a promising anti-cancer agent in low dosages.^[11]

5. *Artemisia Annua* (Asteraceae)

It is also known as sweet wormwood, sweet fern, sweet sage wort sprang. In more recent research artemisin and its derivatives also helps to induce apoptosis of prostate cancer cells and its activity against breast cancer cells, leukaemia, colon and other cancer cells. Artemisinins such as artesunate found to be active against a variety of unrelated tumor cells lines from the most common types such as colon, breast and lung cancers to leukaemias and pancreatic cancer.^[12,13]

6. *Glycyrrhiza Glabra* (Fabaceae)

It is 1m tall commonly known as Licorice. Roots are used for gastrointestinal health and also rich in flavonoids and an antioxidant which acts as a cancer protecting, botanical boosting and an anti-mutagen, which preventing damage to genetic material Glycyrrhizin a triterpenoid saponin isolated from licorice root induce apoptosis in many cell types including human hepatoma, promyelotic leukemia and stomach cancer.^[14,15]

7. *Corcus Sativa* (Iridiaceae)

It is 20-30cm tall commonly known as saffron crocus. Stigmas of the flower contain crocin, anthocyanin, carotene and lycopene and these constituents have various pharmacological effects on different illness. Among all the constituents crocin have anti-cancer activity and basically used for colorectal cancer treatment.^[16]

8. *Viscum Album* (Santalaceae)

Parasitic plant grows on the other trees known as European mistletoe used in cancer treatment for about last several years. Its extracts contain a variety of biologically active compounds. The most thoroughly investigated compounds are the mistletoe lectins and are widely in Gynaecological and Breast-cancer treatment.^[16]

9. *Wedelia Calendula L.* (Asteraceae)

Vitaceae leaf and root used in stomach and lung cancer while flower part used for treating cancer as it contains various anti cancerous compounds.^[16]

10. *Satavari* (Liliaceae)

Shatavari contains saponins, flavonoids, Terpenes and glycosides that possess anti-cancer activity. All these anti-cancer compounds are majorly present in shatavari roots. shatavari roots elevate the antioxidant activity,

antioxidant enzymes and antioxidant defense that fight oxidative stress and reduce the load of free radicals.^[17]

11. *Picrorhiza* (Serophulariaceae)

The therapeutically potent constituents of the drug essentially comprises of three vital bitter glycosides, namely: Picroside I, Picroside II and Kutkoside. Picrorrhiza kurroa (Kutki) used as a hepatoprotective remedy in indian system of medicine, inhibited liver cancer growth formed due to exposure of chemicals in animal studies.

12. *Turmeric* (Zinziberaceae)

Turmeric consists of the dried rhizomes of curcuma longa L. (*C. domestica* Valetton). The active compound in turmeric, curcumin, causes cancer cell death without harming healthy cells. Curcumin helps the body to destroy mutated cancer cells, so they cannot spread through the body and cause more harm. A primary way in which curcumin does so is by enhancing liver function. Curcumin inhibit the synthesis of a protein thought to be instrumental in tumor formation and prevent the development of additional blood supply necessary for cancer cell growth.^[18]

CONCLUSION

Medicinal plants are rich sources of herbal properties contributing in the discovery of new drugs towards various disorders, diseases including cancer without showing no toxic affects on the individuals treated. Treatment of cancer by use of natural products and traditional medicine by applying the concepts of Ayurveda is attaining a great significance scope of cancer research. Medicinal plants contain good immunomodulatory and antioxidant properties which leads them to be a anticancer drug. Only few selected plants have been explored for biological activity from around 1000 species and much more, so further investigations into anticancer activity of the plants showing promising activity, must be undertaken. The less expensive herbal drug treatment may highly be recommended to the rural and poor people to treat effectively the cancers of various type is an ideal choice.

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