

Cancer and Natural Products

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Abstract: Cancer is one of the most common devastating disease affecting millions of people per year. Cancer has been estimated as the second leading cause of death in humans. So there has been an intense search on various biological sources to develop a novel anti-cancer drug to combat this disease. In this review we describe and discuss several approaches to selecting higher plants as candidates for drug development with the greatest possibility of success. We emphasize the role of information derived from various systems of traditional medicine (ethnomedicine) and its utility for drug discovery purposes. Plants have proved to be an important natural source of anti-cancer therapy for several years. With advanced knowledge of molecular science and refinement in isolation and structure elucidation techniques, various anticancer herbs has been identified, which execute their therapeutic effect by inhibiting cancer-activating enzymes and hormones. Several anticancer agents including taxol, vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, and etoposide derived from epipodophyllotoxin are in clinical use all over the world. A number of promising agents such as flavopiridol, roscovitine, combretastatin A-4, betulinic acid and silvestrol are in clinical or preclinical development.

Keywords: Anti-cancer, Herbal medicine, Clinical trials, Cancer treatment

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Introduction

Natural Products, especially plants, have been used for the treatment of various diseases for Thousands of years. Terrestrial plants have been used as medicines in Egypt, China, India and Greece from ancient time and an impressive number of modern drugs have been developed from them. The first written records on the medicinal uses of plants appeared in about 2600 BC from the Sumerians and Akkaidians^[1] According to World Health Organization, 80 % of the people living in rural areas depend on medicinal herbs as primary healthcare system. A great deal of pharmaceutical research done in technologically advanced countries like USA, Germany, France, Japan and China has considerably improved quality of the herbal medicines used in the treatment of cancer. Some herbs protect the body from cancer by enhancing detoxification functions of the body. Some herbs reduce the toxic side effects of chemotherapy and radiotherapy. Scientists all over the world are concentrating on the herbal medicines to boost immune cells of the body against cancer. By understanding the complex synergistic interaction of various constituents of anticancer herbs, the herbal formulations can be designed to attack the cancerous cells without harming normal cells of the body.^[2,3] Cancer is a major public health burden in both developed and developing countries. It was estimated that there were 10.9 million new cases, 6.7 million deaths, and 24.6 million per-sons living with cancer around the world in 2002 (Parkin *et al.*, 2005). Cancer, after cardiovascular disease, is the second leading cause of death^[4,5] in the United States (Hoyert *et al.*, 2005), where one in four deaths is due to cancer. The National Cancer Institute collected about 35,000 plant samples from 20 countries and has screened around 114,000 extracts for anticancer activity (Shoeb, 2005). Of the 92 anticancer drugs commercially available prior to 1983 in the US and among worldwide approved anticancer drugs between 1983 and 1994, 60% are of natural origin (Cragg *et al.*, 1997). Documentation of the Ayurvedic system recorded in Sushruta and Charaka dates from about 1000 BC.^[6] The Greeks also contributed substantially to the rational development of the herbal drugs. Dioscorides, the Greek physician (100 A.D.), described in his work “*De Materia Medica*” more than 600 medicinal plants. Phytochemicals have been proposed to offer protection against a variety of chronic ailments including cardiovascular diseases, obesity, diabetes, and cancer. As for cancer protection, it has been estimated that diets rich in phytochemicals can reduce cancer. The old saying “Prevention is always better than cure” is particularly true in the case of cancer where a cure, if at all possible, is associated with high cytotoxic loads and/or invasive procedures. With our growing understanding of the

molecular etiology of cancer, it has become apparent that strategies which limit DNA damage and/or increase the probability of DNA repair by inhibiting aberrant proliferation will decrease cancer incidence.^[7]

Cancer and its Classification:

Cancer is a general term applied of series of malignant diseases that may affect different parts of body. These diseases are characterized by a rapid and uncontrolled formation of abnormal cells, which may mass together to form a growth or tumor, or proliferate throughout the body, initiating abnormal growth at other sites. If the process is not arrested, it may progress until it causes the death of the organism. The main forms of treatment for cancer in humans are surgery, radiation and drugs (cancer chemotherapeutic agents). Cancer chemotherapeutic agents can often provide temporary relief of symptoms, prolongation of life, and occasionally cures. In recent years, a lot of effort has been applied to the synthesis of potential anticancer drugs. Many hundreds of chemical variants of known class of cancer chemotherapeutic agents have been synthesized but have a more side effects. A successful anticancer drug should kill or incapacitate cancer cells without causing excessive damage to normal cells. This ideal is difficult, or perhaps impossible, to attain and is why cancer patients frequently suffer unpleasant side effects when under-going treatment. However, a waste amount of synthetic work has given relatively small improvements over the prototype drugs. There is a continued need for new prototype-new templates to use in the design of potential chemotherapeutic agents: natural products are providing such templates. Recent studies of tumor-inhibiting compound of plant origin have yielded an impressive array of novel structures^[8].

Types of Cancers:^[9]

1) Cancers of Blood and Lymphatic Systems

a) Hodgkin's disease, b) Leukemias, c) Lymphomas, d) Multiple myeloma, e) Waldenstrom's disease

2) Skin Cancers

a) Malignant Melanoma

3) Cancers of Digestive Systems

a) esophageal cancer, b) Stomach cancer, c) Cancer of pancreas, d) Liver cancer, e) Colon and Rectal cancer, f) Anal cancer

4) Cancers of Urinary system

a) Kidney cancer, b) Bladder cancer, c) Testis cancer, d) Prostate cancer

Causes of Cancer:

The main cause of cancer is mutation; changes in DNA that reduce or eliminate the normal controls over cellular growth, maturation, and programmed cell death. These changes are more likely to occur in people with certain genetic backgrounds (as illustrated by the finding of genes associated with some cases of cancer and familial prevalence of certain cancers) and in persons infected by chronic viruses (e.g., viral hepatitis may lead to liver cancer; HIV may lead to lymphoma). The ultimate cause, regardless of genetic propensity or viruses that may influence the risk of the cancer, is often exposure to carcinogenic chemicals (including those found in nature) and/or to radiation (including natural cosmic and earthly radiation), coupled with a failure of the immune system to eliminate the cancer cells at an early stage in their multiplication. The immunological weakness might arise years after the exposure to chemicals or radiation. Other factors such as tobacco smoking, alcohol consumption, excess use of caffeine and other drugs, sunshine, infections from such oncogenic virus like cervical papillomaviruses, adenoviruses Kaposi sarcoma (HSV) or exposure to asbestos. A Cancer cell also has the character of immortality even in vitro whereas normal cells stop dividing after 50-70 generations and undergoes a programmed cell death (Apoptosis). Cancer cells continue to grow invading nearby tissues and metastasizing to distant parts of the body.

The Mechanism of Cancer Therapy:

- Inhibiting cancer cell proliferation directly by stimulating macrophage phagocytosis, enhancing natural killer cell activity.
- Promoting apoptosis of cancer cells by increasing production of interferon-I, interleukin-2, immunoglobulin and complement in blood serum.
- Enforcing the necrosis of tumor and inhibiting its translocation and spread by blocking the blood source of tumor tissue.
- Enhancing the number of leukocytes and platelets by stimulating the haemopoietic function.
- Promoting the reverse transformation from tumor cells into normal cells.
- Promoting metabolism and preventing carcinogenesis of normal cells.
- Stimulating appetite, improving quality of sleep, relieving pain, thus benefiting patient's health.

Some Promising Plant Derived Anti-cancer Leads:

The first agents to advance into clinical use were the isolation of the vinca alkaloids, vinblastine and vincristine from the Madagascar periwinkle, *Catharanthus roseus* (Apo-cynaceae) introduced a new era of the use of plant material as anticancer agents. They were the first agents to advance into clinical use for the treatment of cancer. Vinblastine and vincristine are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers, including leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma. The discovery of paclitaxel from the bark of the Pacific Yew, *Taxus brevifolia* Nutt. (Taxaceae), is another evidence of the success in natural product drug discovery. Various parts of *Taxus brevifolia* and other *Taxus* species (e.g., *Taxus Canadensis*, *Taxus baccata*) have been used by several Native American Tribes for the treatment of some noncancerous cases [16]. *Taxus baccata* was reported to use in the Indian Ayurvedic medicine for the treatment of cancer. Paclitaxel is significantly active against ovarian cancer, advanced breast cancer, small and non-small cell lung cancer. Camptothecin, isolated from the Chinese ornamental tree *Camptotheca acuminata* (Nyssaceae), was advanced to clinical trials by NCI in the 1970s but was dropped because of severe bladder toxicity. Topotecan and irinotecan are semi-synthetic derivatives of camptothecin and are used for the treatment of ovarian and small cell lung cancers, and colorectal cancers, respectively [17, 18]. Epipodophyllotoxin is an isomer of podophyllotoxin which was isolated as the active antitumor agent from the roots of *Podophyllum* species, *Podophyllum peltatum* and *Podophyllum emodi* (Berberidaceae). Etoposide and teniposide are two semi-synthetic derivatives of epipodophyllotoxin and are used in the treatment of lymphomas and bronchial and testicular cancers [19]. Homoharringtonine isolated from the Chinese tree *Cephalotaxus harringtonia* (Cephalotaxaceae), is another plant-derived agent in clinical use [20]. Combretastatins were isolated from the bark of the South African tree *Combretum caffrum* (Combretaceae). Combretastatin is active against colon, lung and leukemia cancers and it is expected that this molecule is the most cytotoxic phytomolecule isolated so far. [21, 22] The leaf extract of *J. regia* was used to explore its cytotoxic and anti-proliferative activity in an *in-vivo* and *in-vitro* experimental model and proved a potent future drug (Shah and Sharma 2015)

Importance of plant secondary metabolites:

Plant secondary metabolites have proved to be an excellent reservoir of new medical compounds. Many anti-cancer agents have been isolated from various plant sources like *Catharanthus roseus*, *Podophyllum* species, *Taxus brevifolia*, *Camptotheca acuminata*, *Betula alba*, *Cephalotaxus* species, *Erythroxylum pervillei*, *Curcuma longa*, *Ipomoea batatas*, *Centaurea schischkinii* and many others. Scientists are still attempting to explore the bioavailability of anti-cancerous compounds in unexplored plant species.

Anti-cancerous drugs under clinical trials:

Numerous types of bioactive compounds have been isolated from plant sources. Several of them are currently in clinical trials or preclinical trials or undergoing further investigation. There are four major structural classifications of plant-derived anticancerous compounds viz., Vinca alkaloids, Epipodophyllotoxin lignans, Taxane diterpenoids and Camptothecin quinoline alkaloid derivatives. Different anti-cancer compounds that have been identified and reported by scientists and a few of them have been reviewed under.

Vinca alkaloids:

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. Certain semi-synthetic analogues have been developed to increase the therapeutic index. Vinblastine (VLB) and Vincristine (VCR) are the two major naturally occurring active compounds obtained from the Madagascar periwinkle, *Catharanthus roseus* G. Don. (Apocynaceae). These compounds reported potential activity against lymphocytic leukemia in mice. Vinorelbine (VRLB) and Vindesine (VDS) are the two semi synthetic analogs obtained from the active compounds. They showed potential activity against leukemia's, lymphomas, advanced testicular cancer, breast cancer, lung cancer and Kaposi's sarcoma when treated in combination with other chemotherapeutic drugs (Cragg and Newman, 2005). Vinflunine, a bifluorinated derivative of vinorelbine exhibits a superior anti-tumor activity compared to other vinca alkaloids. This novel Vinca alkaloid is currently under Phase II clinical trials. Both Vinflunine and Vinorelbine exhibits reduced toxicity in animal models (Okouneva *et al.*, 2003; Simeons *et al.*, 2008).

Podophyllotoxin:

Podophyllotoxin is obtained from the roots of *Podophyllum* species, namely, *Podophyllum peltatum* Linnaeus and *Podophyllum emodi* Wallich. This was isolated in 1880s, and their structure was elucidated in 1950s. Epipodophyllotoxin is an isomer of podophyllotoxin. The two clinically important semi-synthetic analogs generated from Epipodophyllotoxin are Etoposide and Teniposide which were found very potential in treating lymphomas, bronchial and testicular cancers (Shoeb, 2006).

Taxanes:

Paclitaxel (Taxol®) is obtained from the bark of the Pacific Yew, *Taxus brevifolia* Nutt. (Taxaceae). Their structure was first identified in the year 1971 and they entered the market since 1990s. Another species, *Taxus baccata*, an Indian Ayurvedic medicine have also been in use for cancer therapy (Kingston, 2007). Paclitaxel was found poorly water-soluble and toxic, hence, a watersoluble compound, Docetaxel was derived. Docetaxel (Taxotere®), a semi-synthetic derivative of paclitaxel was found more effective. Docetaxel can be used in patients who are resistant to paclitaxel. Both docetaxel and paclitaxel are used as first- and secondline treatment in patients suffering from metastatic cancer, breast cancer and ovarian cancer. These drugs are also found active against lung cancer, prostate cancer and also lymphoid malignancies. The mechanism of action is that these active agents bind to the polymerized microtubules which prevent the normal mitosis to occur and thus they are called anti-mitotic drugs (Hait *et al.*, 2007).

Camptothecin (CPT):

Camptothecin is a cytotoxic alkaloid isolated mainly from the bark and stem of the Chinese ornamental tree, *Camptotheca acuminata*. It showed poor solubility and severe toxicity, and, because of this reason, certain analogues of CPT were synthesized to overcome these disadvantages. They are topotecan, irinotecan (CPT-11), 9- aminocamptothecin (9-AC), lurtotecan and rubitecan. These analogs work by inhibiting DNA Topoisomerase I which plays a major role in various DNA functions like replication and transcription. It is made up of a pentacyclic ring structure which contains a pyrrole (3, 4 β) quinoline moiety (Srivastava *et al.*, 2005). The camptothecin molecule has an *S*-configured lactone form and a carboxylate form which is responsible for the anti-cancer activity. Topotecan is found clinically effective in patients with epithelial ovarian cancer and small cell lung cancer as a second-line treatment (Creemers *et al.*, 1996). Irinotecan acts as first- and second-line treatment for metastatic colorectal cancer (Fuchs *et al.*, 2006). DX-8951f (Exatecan) is yet another new camptothecin (CPT) derivative which demonstrated potential anti-tumor activity against various tumors both *in-vitro* and *in-vivo* (Mineko *et al.*, 2000). This synthetic analog seems to have better aqueous solubility, tumor efficiency and lesser toxic effects compared to camptothecin and other derivatives (Reichardt *et al.*, 2007). SN-38 (7- ethyl-10 hydroxycamptothecin), an active metabolite of CPT-11 is found to show high cytotoxic activity as compared to CPT-11. Due to the poor solubility of this topoisomerase I inhibitor, it is now designed as a liposome-based formulation. This LE-SN-38 shows increased cytotoxic effects in various cancer cell lines (Zhang *et al.*, 2004). CZ-48 acts as effective anti-cancer agent, with not much toxicity effects in mice. Research is still undergoing for human clinical trials also (Cao *et al.*, 2009).

Herbs with Anticancer Activity:

Allium sativum contains more than 100 biologically useful secondary metabolites, which include alliin, alliinase, allicin, S-allyl- cysteine (SAC), diallyldisulphide(DADS), diallyltrisulphide (DATS) and methylallyltrisulphide. *Aloe vera* contains aloe-emodin, which activates the macrophages to fight cancer. *Aloe vera* also contains acemannan, which enhances activity of the immune cells against cancer. *Aloe vera* is found to inhibit metastases. *Annona species* contain acetogenins, which possess significant cytotoxic activity against leukemia and sarcoma. Acetogenins are found to be effective in the treatment of nasopharyngeal carcinoma. *Arctium lappa* contains potent anticancer factors that prevent mutations in the oncogenes. It has been used in the treatment of malignant melanoma, lymphoma and cancers of the pancreas, breast, ovary, oesophagus, bladder, bile duct and the bone. A study revealed that it reduces the size of tumour, relieves the pain and prolongs the survival period. *Betula utilis* contains betulin that can be easily converted into betulinic acid. Studies have revealed that betulinic acid inhibits growth of malignant melanoma and cancers of the liver and the lung. *Gossypium barbadense* contains gossypol. Recent studies have revealed that gossypol possesses selective toxicity towards cancerous cells. *Gyrophora esculenta* is a mushroom that inhibits growth of cancer by enhancing activity of the natural killer cells. A study revealed that it inhibits carcinogenesis and metastases.

Conclusion

This review paper provides information on herbs and natural products with potential to decrease growth of cancer or be used as adjuvant with cancer treatments for patients who already have or have had cancer. It is documented that medicinal herbs have rich anticancer potential, and on the forefront whenever we talk about anticancer remedies, are significant source of synthetic and/or herbal origin. Natural products discovered from medicinal plants have played an important role in the treatment of cancer. They have exhibited anticancer activity in animal models of leukemia, skin cancer and sarcomas. Through generating awareness regarding usage of herbs and exploring natural product properties, healthcare professionals, can play significant clinical roles as knowledge resources for masses. From information from this review health care professionals can initiate discussion with colleagues to determine whether patient may benefit from from taking a specific herb or natural product. Selected plants have been explored for biological activity and further investigations into

anticancer activity of the plants showing promising activity, must be undertaken. *Vinca rosea* alkaloids, *Vinblastine* and *Vincristine*, are one of the most potent anticancer drugs known. Taxol isolated from *Taxus brevifolia* has figured high in the therapeutic segment of cancer. Cancer being associated with high mortality rates if herbs can be used even in the palliative care or to reduce the side effects associated with cancer would be of great relief for the sufferer. Hence there is hope in the pharmaceutical industry, that even more powerful commercial drugs can be developed sooner, using plant derivatives, to effectively treat cancer and save mankind. This review can help others to explore herbs to further extent and its use in various other disease and toxicity studies along with clinical trials.

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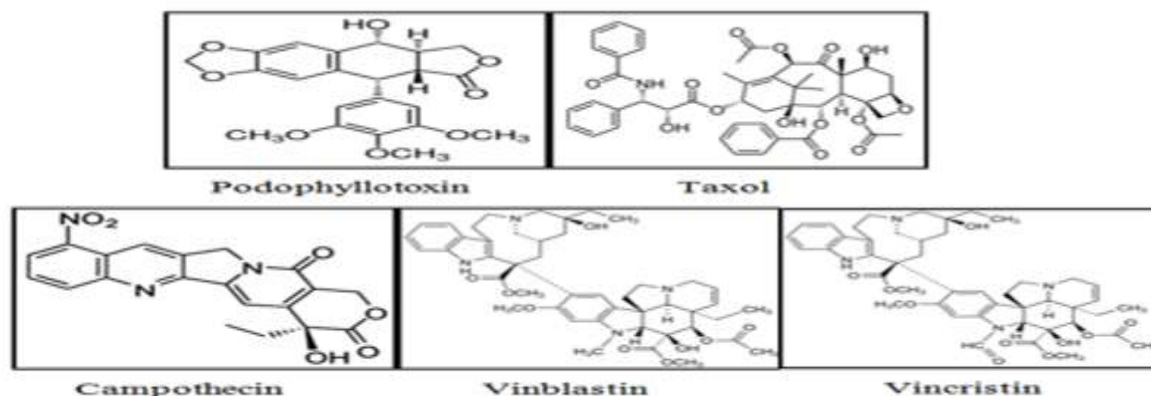


Figure1. Structures of Plant-Derived Anti-Cancer Agents in Clinical Use

Table1. List of plant derivatives used in cancer therapy

Semisynthetic analogs of plant derivatives	Species and Genus name	Experiments on various cancer cells	Mechanism of action	Reference
Vindesine and Vinorelbine	<i>Catharanthus roseus</i>	Leukemias, lymphomas, advanced testicular cancer, breast cancer, lung cancer and kaposi sarcoma.	Mitotic block	Cragg and Newman, 2005
Vinflunine	<i>Catharanthus roseus</i>	Reduced toxicity in animal models	Mitotic block	Okounewa <i>et al</i> , 2003; Simons <i>et al</i> , 2008
Etoposide and Teniposide	<i>Podophyllum peltatum</i> and <i>Podophyllum emodi</i>	Lymphomas, bronchial and testicular cancers.		Shoeb, 2006
Taxol®	<i>Taxus brevifolia</i> Nutt, <i>Taxus baccata</i>	Metastatic, breast, ovarian, lung, prostate cancer and lymphoid malignancies	Anti-mitotic	Kingston <i>et al</i> , 2007
Taxotere®	<i>Taxus brevifolia</i> Nutt, <i>Taxus baccata</i>	Used in patients resistant to Paclitaxel	Anti-mitotic	Hait <i>et al</i> , 2007
Topotecan	<i>Camptotheca acuminata</i>	Epithelial ovarian cancer and small cell lung cancer	DNA topoisomerase 1 inhibition	Creemers <i>et al</i> , 1996
Irimotecan	<i>Camptotheca acuminata</i>	Metastatic and colorectal cancer	DNA topoisomerase 1 inhibition	Fuchs <i>et al</i> , 2006
Exatectan	<i>Camptotheca acuminata</i>	Potential anti-tumor activity both <i>in-vitro</i> and <i>in-vivo</i>	DNA topoisomerase 1 inhibition	Mineko <i>et al</i> , 2000
LE-SN-38	<i>Camptotheca acuminata</i>	Various cancer cell lines	DNA topoisomerase 1 inhibition	Zhang <i>et al</i> , 2004
Curcumin	<i>Curcuma longa</i>	Colorectal cancer, multiple myeloma and pancreatic cancer	Exact mechanism of action is still unknown	Sa <i>et al</i> , 2010; Goel <i>et al</i> , 2008
Emodin	Rhizome of rhubarb	Lung, liver, ovarian and blood cancer	Apoptosis of cancer cells by several pathways	Huang <i>et al</i> , 2009

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