1.1. General introduction to cancer
Cancer is not just one disease, but a group of more than hundred diseases in which a group of cells become abnormal, divide without control and invade other tissues. Cancer cells can spread to other parts of the body through the blood circulation or lymph system. The body is made up of many types of cells which are basic units of life and these cells grow and divide in a controlled way to keep the body healthy. When cells become old or damaged, they die and are replaced with new cells in a programmed way; this process is called as apoptosis. However, sometimes this programmed process goes wrong. The genetic material (DNA) of a cell regulates the normal cell growth and division. If DNA become damaged or changed, producing mutations, cells do not die and cells keep dividing when the body does not need them, these extra cells form a mass of tissue which is called as tumor (Figure-1). Tumors are of two types; one is benign tumor, another one is malignant tumor. Benign tumors are not cancerous, they do not spread to other parts of the body but malignant tumors are cancerous, cells in these tumors can spread to other parts of the body (metastasis).

1.1.1. Classification of cancers
Cancers are classified by the type of cells that constitutes the tumor and, therefore, the tissue presumed to be the origin of the tumor.

- **Carcinoma**: cancer that affects the epithelial tissues that lines internal organs. The most common cancers like breast, prostate, lung and colon cancer come under this category.
- **Sarcoma**: cancer that begins in connective or supportive tissue (e.g., bone, cartilage, fat, muscle, blood vessels).
- **Leukemia**: cancer related to blood-forming tissue.
- **Lymphoma**: cancers that affects the lymphatic tissue.
- **Myeloma**: cancer that begins in bone marrow.
- **Blastoma**: cancer that begins in embryonic tissue.
- **Central nervous system cancers**: cancers that begin in the tissues of the brain and spinal cord.

1.1.2. Nomenclature of cancer
Malignant tumors are usually named using -carcinoma, -sarcoma or -blastoma as a suffix, with the Latin or Greek word for the organ of origin as the root. For example, a cancer of the liver is called hepatocarcinoma; a cancer of the fat cells is called liposarcoma. For
common cancers, the English organ name is used. For example, the most common type of breast cancer is called ductal carcinoma. Here, the adjective ductal refers to the appearance of the cancer under the microscope, resembling normal breast ducts. Benign tumors are named using -oma as a suffix with the organ name as the root. For example, a benign tumor of the smooth muscle of the uterus is called leiomyoma. Unfortunately, some cancers also use the -oma suffix, examples being melanoma and seminoma.

1.1.3. **Cause of cancer**

Cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, chemicals (carbon tetrachloride, benzene, vinyl chloride, asbestos, polychlorinated biphenyls etc.), radiation, infectious agents (viruses/bacteria). Tobacco smoking and chewing is associated with many forms of cancers such as lung, mouth, larynx, head, neck, stomach, bladder, kidney, esophagus and pancreas, particularly 90% of lung cancer is caused due to tobacco smoking. Tobacco smoke contains over fifty known carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons. Prolonged exposure to asbestos fibres is associated with mesothelioma. Radiation such as gamma and X-ray can cause cancer. Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin cancers. It is estimated that 2% of future cancers will be due to current CT scans. Radiation from mobile phones and towers has also been proposed as a cause of cancer, but there is currently little established evidence of such a link. Viruses, bacteria and parasites are responsible for up to 20% of human cancers worldwide. These include HIV causing Kaposi's sarcoma and non-Hodgkin's lymphoma. Hepatitis B virus (HBV) and hepatitis C virus (HCV) causes hepatocellular carcinoma (liver cancer). Human papilloma virus (HPV-16 and 18) causes cervical, vaginal, vulvar, oropharyngeal and penile cancers. Epstein-Barr virus causes burkitt lymphoma, non-Hodgkin lymphoma, Hodgkin lymphoma and nasopharyngeal carcinoma. Kaposi's sarcoma herpes virus (KSHV) causes Kaposi sarcoma. Human T-cell lymphotropic virus type-1 (HTLV1) causes adult T-cell leukaemia. *Helicobacter pylori* cause stomach cancer. Schistosomes (*Schistosoma hematobium*) parasite causes bladder cancer and liver flukes (*Opisthorchis viverrini*) parasite cause liver cancer.

1.1.4. **Cancer-Global and Indian scenario**

Cancer is a leading cause of death in India and other countries. Cancer can affect any part of the human body and people at all ages, but risk for most types cancer increases with age. An estimated 12.7 million new cancer cases and 7.6 million deaths occurred in 2008.
Around 25 million persons are living with cancer around the world (Parkin et al., 2005). Lung, stomach, liver, colon and breast cancer cause the most cancer deaths each year. The most commonly diagnosed cancers worldwide are lung (1.61 million, 12.7% of the total), breast (1.38 million, 10.9%) and colorectal cancers (1.23 million, 9.7%). The most common causes of cancer death are lung (1.38 million, 18.2% of the total), stomach (0.74 million, 9.7%) and liver cancers (0.69 million, 9.2%). Cancer is a major public health burden in both developed and developing countries. About 72% of all cancer deaths in 2007 occurred in low and middle-income countries. Every year about 8,50,000 new cancer cases being diagnosed and about 5,80,000 cancer related death occurs every year in India (Dhanamani et al., 2011). India had the highest number of the oral and throat cancer cases in the world. Deaths from cancer worldwide are projected to continue rising, with an estimated 12 million deaths in 2030.

1.1.5. Cancer treatment
Cancer can be treated by surgery, chemotherapy, radiation therapy and immunotherapy. The choice of therapy depends upon the location/grade of the tumor, stage of the disease and health status. Worldwide people spend several billions of dollars for cancer treatment each year. The economic burden, losses of human life and suffering due to cancer have triggered a concerted effort to fight against this dangerous disease. Although, significant advances have been made in early detection, preventive measures and medical treatment of this disease, much more effort is needed to develop more efficient and safer drugs.

1.1.5.1. Surgery
Surgery is generally used to obtain small samples of tissue for examination and also for the removal of tumors. It is highly effective treatment in eliminating most types of cancer before it has spread to lymph nodes or other sites of the body. If the cancer has not metastasized, surgery may cure the person. Surgery is not the main treatment once a cancer has metastasized and for early-stage cancers surgery is not preferred treatment. The cure through surgical treatment will depend on the size, location and stage of the disease. Because some cancers occur in inaccessible sites and in some cases, necessary organs are required to be removed along with the tumors. In such cases, other treatment methods like radiation and chemotherapy may be preferable.

1.1.5.2. Radiation therapy
Radiation therapy is the treatment of cancer with external beam of radiation. Generally gamma radiation is used for this purpose and in few cases electron or proton beam radiation is also used. These external beams of radiations are focused on the particular
area or organ of the body that contains the cancer. Proton/electron beam radiation, which can be focused on a very specific area, effectively treats certain cancers in areas in which damage to normal tissue is a particular concern, such as the eyes, brain, or spinal cord. External beam radiation therapy is given as a series of equally divided doses over a prolonged period of time. In other radiation therapy strategies, a radioactive substance may be injected into a vein to travel to the cancer (for example, radioactive iodine, which is used in treatment of thyroid cancer). Another technique uses small pellets (seeds) of radioactive material placed directly into the cancer (for example, radioactive palladium used for prostate cancer). These implants provide intense radiation to the cancer, but little radiation reaches surrounding tissues. Implants contain short-lived radioactive substances that stop producing radiation after a period of time.

Radiation therapy plays a key role in curing many cancers, including Hodgkin lymphoma, early-stage non-Hodgkin lymphoma, squamous cell cancer of the head and neck, seminoma (a testicular cancer), prostate cancer, early-stage breast cancer, some forms of non small-cell lung cancer, brain and spinal cord tumor. Even though several precautions have been taken to avoid overexposing the radiation on normal tissue, it can damage normal tissues near the tumor. Particularly radiation greatly damages the skin, bone marrow, hair follicles, and the lining of the mouth, esophagus, intestine and ovaries/testes.

1.1.5.3. Immunotherapy

The immune system enables our body to recognize and attack foreign materials allowing it to fight off infection and disease. It also enables our bodies to recognize abnormal cells and to respond quickly by destroying them. Cancer immunotherapy is used to stimulate the body's immune system against cancer. For example, vaccines composed of antigens derived from tumor cells can boost the production of antibodies or immune cells (T lymphocytes). Cancer vaccines are of two types, one is preventive vaccine and another one is therapeutic vaccine. The U.S. Food and Drug Administration (FDA) has approved two preventive vaccines (Gardasil and Cervarix), that protect against infection by HPV-16 and HPV-18 that cause approximately 70% of all cases of cervical cancer worldwide. HPV-16 and HPV-18 also cause some vaginal, vulvar, anal, penile, and oropharyngeal cancers (Doorbar, 2006; Parkin, 2006). In April 2010, the U.S. FDA has approved the first cancer vaccine (Sipuleucel-T) for the treatment of metastatic prostate cancer in men. Presently several cancer vaccines are under clinical trials for the treatment or prevention of various cancers.
1.1.5.4. Chemotherapy

Chemotherapy is the treatment of cancer with drugs and chemotherapy is the widely used method for the treatment of cancer. An ideal drug should destroy cancer cells without harming normal cells; however most drugs are nonselective. Instead, drugs are designed to inflict greater damage on cancer cells than on normal cells, typically by using drugs that affect a cell's ability to grow. However, because normal cells also need to grow, and some grow quite rapidly (such as those in the bone marrow and those lining the mouth and intestine), all chemotherapy drugs affect normal cells and cause side effects.

One new approach to limit the side effects and increase the effectiveness of anticancer drugs uses a variety of "molecularly targeted" drugs. These drugs kill cancer cells by attacking specific pathways and processes vital to the cancer cells survival and growth. For example, cancer cells need blood vessels to provide extra oxygen and nutrients. Some drugs can block blood vessel formation to cancer cells or the master signalling pathways that control cell growth. Common side effects associated with cancer chemotherapy are nausea, vomiting, loss of appetite, hair loss, weight loss, fatigue, and low blood cell counts that lead to anaemia and increased risk of infections.

There are many different chemotherapy drugs, some derived from natural, and some from synthetic sources, however natural product derived drugs are predominate. In view of the several side effects associated with the existing anticancer drugs there is an urgent need for new drugs which are less toxic and more specific towards cancer cells.

1.2. Natural products in folk medicine

Natural products, derived from plant sources have been used to treat various human disease since the dawn of medicine. Plant and animal based medicines have been used in India, China, Japan, Egypt, and Greece since ancient times and several 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 (Samuelsson, 1999). The Egyptian “Ebers Papyrus” from about 1552 B.C. is one of the oldest preserved medical documents. It contains 700 formulas and folk remedies. The Chinese *Materia Medica*, which describes more than 600 medicinal plants, has been well documented with the first record dating from about 1100 BC (Cragg *et al.*, 1997). The Greek *De Materia Medica*, which describes more than 600 medicinal plants, has been well documented with the first record dating from about 100 AD (Samuelsson, 1999). Indian Ayurveda is one of the oldest traditional medical practices and it is well documented with *Susruta* and *Charaka Samhita* dating from about 1000 BC (Kappor, 1990). These two well-known ayurvedic
classics contain description of 1120 illnesses, 700 medicinal plants, and a detailed study on anatomy. *Charaka* and *Sushruta Samhitas*, describe cancer as inflammatory or non-inflammatory swelling and mention them as either *granthi* (minor neoplasm) or *arbuda* (major neoplasm). During the 7th century BC, Atreya and Dhanwantari used herbal medicines for treating the early stages of cancer and surgery in advanced cases. In the 8th century AD, Vagbhata, a Buddhist physician composed two texts: *Astanga Hridaya* and *Astanga Sangraha* in which he described new methods for cancer treatment. Other ayurvedic texts of internal medicine, *viz.*, *Chakradatta* composed by Chakrapani (10th century AD), the *Sarangadhara Samhita* by Sarangadhara (14th century AD), the *Bhavaprakasha Samhita* by Bhavamisra (15th century AD), the *Satmya Darpan Samhita* by Viswanath (16th century AD), the *Vaisajya Ratnabali* by Binoda Lala Sen Gupta (18th Century AD), the *Rasatarangini* by Sadananda Sharma (19th century AD), etc. explain numerous remedies to treat internal and external neoplasm’s. In Indian ayurveda several herbs have been used in the treatment of cancer. For example *Amorphopallus campanulatus*, *Baliospermum montanum*, *Barleria prionitis*, *Basella rubra*, *Curcuma domestica*, *Ficus bengalensis*, *Flacourtia romantchi*, *Madhuca indica*, *Moringa oleifera*, *Oxosxylum indicum*, *Pandanus odoratissimum*, *Pterospermum acerifolium*, *Raphanus sativus*, *Prosopis cineraria*, *Vitis vinifera* (Patwardhan et al., 2004; Premalatha and Rajgopal, 2005; Rao et al., 1999). Even today most of the Indians and Chinese rely on traditional medicine for their primary health care and consider it as cheapest & safest.

Plants have long been used in the treatment of cancer (Hartwell, 1982). Of the 79 FDA approved anticancer drugs from 1983-2002, 60% are either natural products or natural product derived.

**1.3. Natural product derived anticancer agents in clinical use**

Vinblastine and vincristine (Figure-2) are vinca alkaloids found in the Madagascar periwinkle, *Catharanthus roseus* (formerly known as *Vinca rosea*). These two natural products are approved by United States Food and Drug Administration (US FDA) for the treatment of cancers like leukemia, lymphomas, Hodgkin’s lymphoma, breast cancer, acute lymphoma, soft tissue sarcomas, multiple myeloma and neuroblastoma (Cragg and Newman, 2005). Vinblastine and vincristine are antimicrotubule agents which led to a new era of the use of plant material as anticancer agents. These discoveries prompted the United States National Cancer Institute (NCI) to initiate an extensive plant collection program. Approximately 35,000 plant samples from 20 countries were collected that
providing 1.14,000 different extracts, which were screened for anticancer activity (Shoeb, 2006).

Taxol commonly known as paclitaxel is a diterpenoid. It was first isolated in 1966 from the Pacific yew, *Taxus brevifolia* in Washington State as part of a random collection program by the U.S. Department of Agriculture for the National Cancer Institute (Wani et al., 1971; Rowinsky et al., 1992). Later on, it was isolated from several other species of Taxus including *Taxus wallichiana*, the Himalayan yew. Paclitaxel is a blockbuster anticancer drug which is in clinical use for the treatment of refractory ovarian cancer, metastatic breast and lung cancer and Kaposi's sarcoma. It acts as microtubulin stabilizing agent. The use of various parts of *T. brevifolia* and other *Taxus* species (e.g. *T. canadensis* Marshall, *T. baccata* L.) by several Native American tribes for the treatment of some non-cancerous conditions has been reported, while the leaves of *T. baccata* are used in the Indian ayurveda for the treatment of cancer. The discovery of paclitaxel is another example of the success of natural product drug discovery. The main problem is the availability of the taxol (the bark of *T. brevifolia* contains only trace amounts of taxol, 0.01–0.03%; in addition, the collection of the bark from the tree is associated with death of the plant source), which was overcome by the development of a semi-synthetic production process, that is based on the natural product 10-deacetyl baccatin III (10-DAB) as a readily available precursor. 10-DAB is available in sufficient quantities from the regenerating needles of the fast growing European yew tree (*T. baccata*); elaboration of this precursor into taxol involves reaction with a synthetic β-lactam (comprising the C13 side chain) and can be achieved in seven chemical steps. Production of taxol through plant cell culture has been attempted with some success and research is in progress to optimize the yields to evolve the process as possible alternative to isolation from Yew tree needles.

Systematic chemical modifications of natural products is used to produce analogues with greater pharmacological activity, improved bio-availability and with fewer side effects. For example, docetaxel commonly known as taxotere is semi synthetic derivative of taxol, which is in clinical use for the treatment of locally advanced or metastatic breast and lung cancer. It also has better pharmacological properties such as improved water solubility, and acts on the microtubules. It enhances polymerization of tubulin into stable microtubule bundles leading to cell death. Taxotere is now known as a better anticancer drug than taxol. Cabazitaxel is a semisynthetic derivative of taxol approved by the U.S.
Food and Drug Administration (FDA) for the treatment of hormone-refractory prostate cancer.

Based on the SAR of taxol, several analogues have been generated (Figure-4). According to the Adis R&D insight database, eight taxol derivatives are under clinical trials stage (BMS-184476, 188797, 275183, taxoprexin, TL-00139, DJ-927, RPR-109881A and ortataxel) (Choy et al., 1998; Nicoletti et al., 2000; Polizzi et al., 2000; Ali et al., 2001; Altstadt et al., 2001; Rose et al., 2001; Vredenburg et al., 2001; Cisternino et al., 2003; Mastalerz et al., 2003; Sampath et al., 2003; Shionoya et al., 2003).

Homoharringtonine isolated from the Chinese tree *Cephalotaxus harringtonia var drupacea* (Cephalotaxaceae), is another plant-derived agent in clinical use (Itokawa et al., 2005; Powell et al., 1970). A racemic mixture of harringtonine and homoharringtonine has been used successfully in China for the treatment of acute myelogenous and chronic leukemia (Cragg and Newman, 2005; Kantarjian et al., 1996). Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin and valrubicin) are well known anticancer drugs which are derived from Streptomyces bacteria (Figure-4). These anthracyclines are useful in the treatment of leukaemia, lymphoma, breast-, uterine-, ovarian- and lung-cancers.

Camptothecin (Figure-3) is an alkaloid, which was first isolated from the Chinese ornamental tree *Camptotheca acuminata*, also known as the tree of joy and tree of love. It has also been isolated from *Ophiorrhiza pumila* and *Mapia foetida*.

Camptothecin is a potent cytotoxic agent (Cragg and Newman, 2005). It shows anticancer activity mainly for solid tumors. It inhibits DNA topoisomerase-I and exhibits anticancer activity mainly against colon and pancreatic cancer cells. Camptothecin was advanced to clinical trials by the NCI in the 1970s, but was dropped because of severe bladder toxicity. However, extensive research was performed by pharmaceutical companies in a search for more effective camptothecin derivatives and topotecan, developed by Glaxo SmithKline, and irinotecan, originally developed by the Japanese company, Yakult Honsha, are now in clinical use. Topotecan is used for the treatment of ovarian and small-cell lung cancers, while irinotecan is used for the treatment of colorectal cancers. Similarly cyclo lignan podophyllotoxin which is isolated from *Podophyllum peltatum* and *Podophyllum hexandrum* is a highly toxic molecule and it is not being used in the treatment of cancer, but its semi synthetic derivatives such as etoposide and teniposide are in clinical use (developed by Sandoz Laboratories in the 1960s and 1970s) for the treatment of various
cancers like testicular, small-cell lung cancer, lymphoma, leukemia and Kaposi’s sarcoma. Elliptinium is a derivative of ellipticine, isolated from a Fijian medicinal plant *Bleekeria vitensis* is marketed in France for the treatment of breast cancer (Cragg and Newman, 2005).

**1.4. Natural product derived anticancer agents in clinical development**

The combretastatins were isolated from the South African “bush willow”, *Combretum caffrum* (Combretaceae), collected in Southern Africa in the 1970s for the NCI by the USDA, working in collaboration with the Botanical Research Institute of South Africa. These collections were part of a random collection program aimed at the discovery of novel anticancer agents. Species of the *Combretum* and *Terminalia* genera, both of which belong to the Combretaceae family, are used in African and Indian traditional medicine for the treatment of a variety of diseases, including hepatitis and malaria. Several *Terminalia* species have reportedly been used in the treatment of cancer. Combretastatin A-4 is the most potent naturally occurring combretastatin known, its phosphate prodrug (CA-4-P) in combination with paclitaxel/carboplatin is under phase III clinical trial for the treatment of anaplastic thyroid cancer (Ohsumi *et al.*, 1998; Pettit *et al.*, 1995). There is currently no fully FDA approved treatment for this form of cancer. Combretastatin A-4 is known as an antimicrotubule agent acting at the colchicine-binding site on tubulin. Combretastatin A-4 is active against colon, lung and leukemia cancers and it is expected that this molecule is the most cytotoxic phyto-molecule isolated so far (Ohsumi *et al.*, 1998; Pettit *et al.*, 1995).

Betulinic acid, a pentacyclic triterpene, is a common secondary metabolite of plants, primarily from *Betula* species (Betulaceae) (Cichewitz *et al.*, 2004). Betulinic acid was also isolated from *Zizyphus* species, e.g. *mauritiana*, *rugosa* and *oenoplia* (Pisha *et al.*, 1995; Nahar *et al.*, 1997) and displays selective cytotoxicity against human melanoma cell lines (Balunas *et al.*, 2005).

Epothilones (A-F) (Figure-5) are isolated from common soil bacteria *Sporangium cellulosum* in 1980’s by Hofle and Reichenbach. Epothilones inhibits microtubules function. All the epothilones (A-F) are in clinical trials stage against various cancers and epothilone-B (ixabepilone) is in clinical use for aggressive metastatic and advanced breast cancer treatments. Pervilleine A is isolated from the roots of *Erythroxylum pervillei* Baill. (Erythroxylaceae) (Silva *et al.*, 2001). Pervilleine-A was selectively cytotoxic against a multidrug resistant (MDR) oral epidermoid cancer cell line (KB-V1) in the presence of the anticancer agent vinblastine (Mi *et al.*, 2001). Pervilleine A is currently in preclinical
development (Mi et al., 2003). Silvestrol was first isolated from the fruits of *Aglaia silvestris* (Hwang et al., 2004). Silvestrol exhibits cytotoxicity against lung and breast cancer cell lines (Cragg and Newman, 2005). Biological studies are ongoing to determine the mechanism(s) of action for silvestrol. Flavopiridol is a synthetic flavone, derived from the plant alkaloid rohitukine, which was isolated from *Dysoxylum binectariferum* (Meliaceae) (Kellard et al., 2000). It is currently in phase I and II clinical trials against a broad range of tumors, including leukemia, lymphomas and solid tumors (Christian et al., 1997). The synthetic agent roscovitine which is derived from natural product olomucine, originally isolated from *Raphanus sativus* L. (Brassicaceae), is in Phase II clinical trials in Europe (Cragg and Newman, 2005; Meijer et al., 2003).

Even though nature provides innumerable primary leads in their diverse structural types, stereochemistry, a limited number of natural products have been modified so far by chemical methods. Thus, most original compounds still await full exploitation of their structures. Moreover, the majority of the isolated compounds were never investigated systematically with regard to their mode of action and their specific target interaction. We may add here that every natural molecule is an "untreated diamond" waiting for cutting and refining. Undoubtedly, chemical modification of a given structure of a natural product is often more rewarding than the tedious and time-consuming synthesis of recurrent skeletons and homologues. There are several reports available on podophyllotoxin and camptothecin derivatives in literature, in which these derivatives have showed better anticancer activity than etoposide, teniposide, topotecan etc., this clearly shows there are still possibilities in the development of drug candidates from these molecules. There are thousands of unexploited plants waiting for the screening of anticancer activity. Screening and refining the structures will yield possible drug candidates.

1.5. **Drug delivery vehicles in cancer chemotherapy**

Even though several aforementioned natural products and their derivatives have been used as life saving drugs in cancer chemotherapy, most of these molecules are associated with severe mammalian toxicity owing to their nonspecific mode of action. An ideal anticancer drug would only destroy the cancer cells without harming the normal cells or their functions. The discovery and development of new drugs is a time-consuming and expensive process.
Figure-1: Cell division in normal cells and cancer cells

Figure-2: Natural product derived molecules which are in clinical use as anticancer drugs.
Figure-3: Natural product derived molecules which are in clinical use as anticancer drugs.
15. Taxol, $R_1 = \text{Ph}$, $R_2 = \text{H}$
16. Docetaxel, $R_1 = \text{Me}_3\text{CO}$, $R_2 = \text{H}$
17. Carbazitaxel, $R_1 = \text{Me}_3\text{CO}$, $R_2 = \text{CH}_3$
18. BMS-184476: $R_1 = \text{CH}_2\text{SCH}_3$, $R_2 = \text{CH}_3$
19. BMS-188797: $R_1 = \text{H}$, $R_2 = \text{OCH}_3$
20. TL-00139
21. RPR-109881A
22. Ortataxel
23. Taxoprexin
24. DJ-927
25. BMS-275183

**Figure-4**: Few taxol derived molecules which are in clinical development as anticancer drugs.
Figure-5: Few natural product derived molecules which are in clinical development as anticancer drugs.
Each new candidate is estimated to take around 10-15 years to bring it from conception to market, with a cost of more than $500 million. Some problems associated with currently available anticancer drugs is toxicity (no selectivity), low water solubility, poor bioavailability, poor absorption etc. All these problems can be solved using suitable drug delivery vehicles attached to anticancer compounds.

Several nanoparticles (polymer and liposome) and peptide based drug delivery vehicles have been found to be effective for such a combination therapy.

1.5.1. Nanoparticles as drug delivery vehicles

The fate of a drug after administration in vivo is determined by a combination of several processes, such as distribution, metabolism and elimination when given intravenously or absorption, distribution, metabolism and elimination when an extra vascular route is used. The result depends mainly on the physicochemical properties of the drug and therefore on its chemical structure. Nanoparticles play a very important role in cancer research. Due to extremely small size of nanoparticles they are easily and more readily taken up by the human body. Biological membranes and access cells, tissues and organs are eligible for entrance of nanoparticles. These cells are not able for cross by the larger-sized particles. Nanoparticles are stable, solid colloidal particles consists of biodegradable polymer or lipids and size range 10-1000 nm. Nanoparticles loaded with anticancer agents can successfully increase drug concentration in cancer tissues and also act at cellular levels, enhancing antitumor efficacy.

1.5.1.1. Polymeric nanoparticles

Naturally occurring polymers such as albumin, chitosan, and heparin are becoming increasingly important in the field of drug delivery (Felix, 2008). In 2005, a nanoparticle formulation of albumin bound paclitaxel (abraxane), was approved by U.S. FDA for breast cancer treatment, in which serum albumin is included as a carrier (Gradishar et al., 2005). Besides breast cancer, abraxane has also been evaluated in clinical trials involving many other cancers including non-small cell lung cancer and recently positive results were published from phase-III clinical trials for the treatment of non-small cell lung cancer (Nyman et al., 2005; Green et al., 2006). Several synthetic polymers such as N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA), polystyrene-maleic anhydride copolymer, polyethylene glycol (PEG), and poly-L-glutamic acid (PGA) have been developed for drug delivery. Among all these synthetic polymers PGA was the first biodegradable polymer to be used for conjugate synthesis (Li, 2002). Several
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representative chemotherapeutics that are used widely in the clinic have been tested as conjugates with PGA *in vitro* and *in vivo* and showed encouraging results (Li, 2002). Among them, Xyotax (PGA-paclitaxel) and CT-2106 (PGA-camptothecin) are now in clinical trials (Bhatt *et al.*, 2003; Sabbatini *et al.*, 2004). HPMA and PEG are the most widely used non biodegradable synthetic polymers (Duncan, 2003). PK1, which is a conjugate of HPMA with doxorubicin, was the synthetic polymer-drug conjugate that completed Phase-I clinical trials (Vasey *et al.*, 1999).

1.5.1.2. Polymeric micelles

The functional properties of micelles are based on amphiphilic block copolymers, which assemble to form a nano-sized core/shell structure in aqueous media. The hydrophobic core region serves as a reservoir for hydrophobic drugs, whereas the hydrophilic shell region stabilizes the hydrophobic core and renders the polymers water-soluble, making the particle an appropriate candidate for i.v. administration (Adams *et al.*, 2003). The drug can be loaded into a polymeric micelle in two ways: physical encapsulation (Batrakova *et al.*, 1996) or direct attachment (Nakanishi *et al.*, 2001). The first polymeric micelle formulation of paclitaxel, Genexol-PM (PEG-poly(D,L-lactide)-paclitaxel), is a cremophor-free polymeric micelle-formulated paclitaxel, a phase I and pharmacokinetic study has been conducted in patients with advanced refractory malignancies (Kim *et al.*, 2004). Multifunctional polymeric micelles containing targeting ligands and imaging and therapeutic agents are being actively developed (Nasongkla *et al.*, 2006) and will become the mainstream among several models of the micellar formulation in the near future.

1.5.1.3. Dendrimers

Dendrimers are a family of nanosized, three-dimensional polymers characterized by a unique tree-like branching architecture and compact spherical geometry in solution. Their name is derived from the Greek word “dendron”, which means “tree”. Dendrimers are first discovered in the early 1980’s by Tomalia *et al* (1985). The inherent stability of dendritic micelles, as well as their ability to encapsulate guest molecules, makes them good candidates for the design of novel drug delivery agents.

A dendrimer is a synthetic polymeric macromolecule of nanometer dimensions, composed of multiple highly branched monomers that emerge radially from the central core. Properties associated with these dendrimers such as their monodisperse size, modifiable surface functionality, multivalency, water solubility, and available internal cavity make them attractive for drug delivery (Svenson and Tomalia, 2005). Polyamidoamine dendrimer, most widely used as a scaffold, was conjugated with cis-
platin (Malik et al., 1999). The easily modifiable surface characteristic of dendrimers enables them to be simultaneously conjugated with several molecules such as imaging contrast agents, targeting ligands, or therapeutic drugs, yielding a dendrimer-based multifunctional drug delivery system (Svenson and Tomalia, 2005).

1.5.1.4. Liposomes
Liposomes are hollow structures, composed of a lipid bilayers and an internal aqueous pool. Liposomes can be filled with drugs, and used to deliver drugs for cancer and other diseases also. Liposomes improve the solubility of lipophilic drugs that would otherwise be difficult to administer intravenously. Liposomes can also prolong the duration of drug exposure by controlled release of the drug. Liposomes can even protect a drug against degradation and also reduces the side effects of the encapsulated drug. For example, the dose limitation of the cytotoxic drug doxorubicin is its (irreversible) damage to heart muscles. Liposome encapsulation greatly reduces exposure of the heart to doxorubicin and thereby its cardiotoxicity. Several liposomal chemotherapeutics are in clinical use viz., doxorubicin (doxil, myocet) and daunorubicin (daunoxome) are approved for the treatment of metastatic breast cancer and AIDS-related Kaposi’s sarcoma (Rosenthal et al., 2002; Rivera, 2003; Markman, 2006). Several liposomal chemotherapeutics are currently being evaluated in clinical trials (Hofheinz et al., 2005).

1.5.2. Tumor specific peptides as drug delivery vehicles
Tumor specific peptides are considered as an important class of drug delivery vehicles in cancer chemotherapy. Tumor blood vessels express molecular markers that distinguish them from normal blood vessels (Laakkonen et al. 2002). Many of these tumor vessel markers are related to angiogenesis, but some are selective for certain tumors (Rouslahti, 2002). Tumor specific peptides selectively recognize these markers and therefore accumulate at the tumor site. Tumor specific peptides also exhibit anticancer property and these peptides also useful to improve the water solubility of the drug. We can use these tumor homing peptides as carriers for tumor specific drug delivery. Anchoring anticancer drug to tumor homing peptides with a suitable linker will improve the selectivity, efficiency, water solubility and decrease the dosage of the drug. Several anticancer drugs like chlorambucil (Myrberg et al., 2008), doxorubicin (Arap et al., 1998), cisplatin (Sumitra et al. 2008; Cohen and Lippard, 2001) etc. have been successfully conjugated with tumor specific peptides.
1.6. Conclusion
A majority (> 60%) of all the FDA approved anticancer drugs are either natural products or their analogues, demonstrating the important role in the development of new anticancer drugs. Drug delivery vehicles play an important role in the cancer chemotherapy for the reduction of dosage of anticancer drugs and consequently, reduction of toxicity of these drugs towards normal cells.

1.7. References


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