Introduction
1. Introduction

1.1 Cancer:

Cancer is the name given to a large group of diseases, all of which have one thing in common: cells that grow out of control. Normally, the cells that make up all the parts of our body go through a predictable life cycle — old cells die and new cells arise to take their place. Occasionally, this process goes awry and cells begin to multiply out of control. The end result is a mass of cells, called a tumor. A benign tumor is one that does not spread, or metastasize to other parts of the body. It is considered noncancerous. A malignant tumor, on the other hand, can spread throughout the body and is considered cancerous. When malignant cells break away from the primary tumor and settle into another part of the body, the resulting new tumor is called either a metastasis or a secondary tumor. (Sarkar, 2009).

Cancer is actually a group of many related diseases that all have to do with the cells. Cells are the very basic units that make up all living things, including the human body. There are billions of cells in human body. Normal body cells grow and divide, unlike normal cells, cancer cells just continue to grow and divide out of control. Cancer cells usually group or clump together to form tumors. A growing tumor becomes a lump of cancer cells that can destroy the normal cells around the tumor and damage the body's healthy tissues. Sometimes cancer cells break away from the original tumor and travel to other areas of the body, where they are lodged and keep growing to form new tumors. This is how cancer spreads. The spread of a tumor to a new place in the body is called metastasis (Fayed Lisa, 2009).

1.1.1 Type of cancer:

There are many different types of cells in the body and all these different cells can grow into cancer either benign or malignant. Cells from different body parts do behave differently and some may grow faster or some slower, some produce different symptoms, others respond differently to the same treatment and some are likely to spread to a specific part of the body. Cancers are divided into four main groups according to the body tissue from which they arise (Table 1.1) (Bagchi and Preuss, 2005).
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Table 1.1: Cancer Terminology:

<table>
<thead>
<tr>
<th>Carcinoma</th>
<th>Epithelial cells, such as the cells that line the Digestive tract and make up organs such as the liver, kidney and pancreas.</th>
<th>Glandular- e.g., Prostate adenocarcinoma, Squamous- e.g., Carcinoma of Cervix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoma</td>
<td>Cells that form things such as muscle, nerves, or blood vessels.</td>
<td>Leiomyosarcoma- hyper proliferation of smooth muscle is called a leiomyoma, Osteosarcoma- Bone, Liposarcoma- hyper proliferation of fat cells is called a lipoma</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Cells in a lymph gland</td>
<td>Solid tumor- From B or T-lymphocytes</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>Blood-forming tissue</td>
<td>Myelocytic- Myeloid cells: Lymphocytic leukaemia, Leukaemia Lymphocytes (white blood cells)</td>
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</table>

1.1.2 Multidrug resistance in cancer

One of the major limitations of long term chemotherapeutic treatment is the development of drug resistance; while some cancer cells are intrinsically resistant to various anticancer drugs, others ‘develop’ resistance to multiple chemotherapeutic drugs upon treatment, a phenomenon known as ‘Multi Drug Resistance’ (MDR). Those cancer cells which are inherently resistant to multiple anticancer agents on prolonged administration of the drugs, there is an increase in the expression of different classes of proteins involved in drug metabolism, detoxification and active drug efflux in addition to alteration of intracellular drug targets, to which the drug binds. All these mechanisms alter the effective drug concentration within a cell. These mechanisms are also known to be activated in the cancer cells which ‘acquire’ drug resistance. One of the immediate measures the cell utilizes towards drug resistance is, the active efflux of the drug so as to minimize the number of molecules of the drug entering the cell. This is usually a cell membrane based mechanism, where a family of plasma membrane efflux transporters are.
overexpressed. These include the most common ATP-binding cassette (ABC) transporters, which have received extensive attention (Litman et al, 2001). These transmembrane protein transporters actively extrude the cytotoxic drugs by utilizing ATP. There are several subclasses of these transporters, the most well characterized in cancer being ABCB1 or MDR1 (P-glycoprotein), ABCC1 (MRP1) and ABCG2, also known as BCRP as it was discovered in a breast cancer cell line (Gottesman and Ling, 2006). These transporters are not specific to a particular class of molecules and show a wide spectrum of substrate recognition and binding. The substrates these bind to vary from ions, bile salts, anticancer drugs, microbial toxins and hydrophobic compounds, like those derived from plants.

1.1.3 The Mechanism on Cancer Therapy (Cancer.gov)

1. Inhibiting cancer cell proliferation directly by stimulating macrophage phagocytosis, enhancing natural killer cell activity.

2. Promoting apoptosis of cancer cells by increasing production of interferon, interleukin-2 immunoglobulin and complement in blood serum.

3. Enforcing the necrosis of tumor and inhibiting its translocation and spread by blocking the blood source of tumor tissue.

4. Enhancing the number of leukocytes and platelets by stimulating the hemopoietic function.

5. Promoting the reverse transformation from tumor cells into normal cells.

6. Promoting metabolism and preventing carcinogenesis of normal cells.

7. Stimulating appetite, improving quality of sleep, relieving pain, thus benefiting patients health.

1.1.4 Cancer globally:

The burden of cancer is high and is increasing worldwide. One in eight deaths worldwide is due to cancer. Globally, cancer cause more death than AIDS, T.B and malaria.
combined. Cancer is second leading cause of death in economically developed countries and third leading cause of death in developing countries (Jemal et al, 2008).

Each year cancer is newly diagnosed in 10 million people worldwide and account for 7.1 million deaths (12.5% of the global total). According to the World Health Organization (WHO) global cancer rates could increase by 50% to 15 million by 2020 (WHO, 2013). This sharp and alarming increase in cancer rates both in developed and developing is due to steadily aging populations in countries, present trends in smoking prevalence along with the growing adoption of unhealthy lifestyles (WHO, 2013). According to Globocan 2012, an estimated 14.1 million new cancer cases and 8.2 million cancer related deaths occurred in 2012. When compared with 12.7 million and 7.6, respectively, in 2008.

The GLOBCAN 2012 predicted substantive increase to 19.3 million new cancer cases per year by 2025. In developing countries cancer has appeared as a main public health problem. However, the likelihood of being diagnosed with cancer in developed countries is twice as high as in developing countries. The highest overall cancer rates for industrial nations are: United States of America (USA), Italy, Australia, Germany, The Netherlands, Canada and France, and the lowest cancer rates for developing countries were Northern Africa, Southern and Eastern Asia (WHO, 2012).

Lung cancer is the most common cancer worldwide, accounting for 1.2 million new cases annually, for which the main cause is smoking and other causes include domestic and industrial pollution. A clear linear dose-response relationship exists between magnitude of cancer and the period of smoking as well as the amount smoked (http://www.doh.gov.za/docs/research/vol5-4cancer.html). One should however note that the three leading killers differ from the three most common forms of cancer. Of all the cancer deaths in the world, according to the (WHO, 2012) the three leading killers are: lung cancer (17.8 %), stomach cancer (0.4 %) and liver cancer (8.8 %). More than a quarter of deaths are attributed to cancer in many countries. As many as one third of cancers worldwide could be prevented by healthy lifestyle and discouraging the use of tobacco is the most preventable cause of cancer in the world. Childhood cancers (aged one to 14) are rare and largely curable if detected early through modern molecular and imaging technology e.g. PET scanning for lymphomas, the treatment options is limited. Cancer causes the second most deaths, in children worldwide. Three out of five children
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(80 116 or 92%) still die in developing countries because of cancer and 133 931 (83%) cases are newly diagnosed each year. In developed countries childhood cancers are newly diagnosed in 26 864 (17%) children and account for 6 863 deaths annually (IARC, 2002).

1.1.5 India- cancer statistics (Dikshit et al, 2012)

In India 556 400 cancer deaths occurred in 2010. 395 400 (71%) deaths occurred in people aged between 30–69 years (200 100 men and 195 300 women). At 30–69 years, the three most common fatal cancers were oral (including lip and pharynx, 45 800), stomach (12·6%), and lung (including trachea and larynx, (11·4%) in men, and cervical (17·1%), stomach (14·1%), and breast (10·2%) in women. Tobacco-related cancers represented 42·0% in male and 18·3% in female cancer deaths and there were twice as many deaths from oral cancers and lung cancers.

1.2 Herbal medicine

The World Health Organization (WHO) has recently defined traditional medicine (including herbal drugs) as comprising therapeutic practices that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today. Traditional medicine is the synthesis of therapeutic experience of generations of practicing physicians of indigenous systems of medicine. The traditional preparations comprise medicinal plants, minerals, organic matter etc. Herbal drugs constitute only those traditional medicines which primarily use medicinal plant preparations for therapy. The earliest recorded evidence of their use in Indian, Chinese, Egyptian, Greek, Roman and Syrian texts dates back to about 5000 years. The classical Indian texts include Rigveda, Atherveda, Charak Samhita and Sushruta Samhita. The herbal medicines/traditional medicaments have, therefore, been derived from rich traditions of ancient civilizations and scientific heritage (Kamboj, 2000).

In 1991 WHO developed guidelines for the assessment of herbal medicine (WHO, 1991). The salient features of WHO guidelines are:

(i) Quality assessment: Crude plant material; Plant preparation; finished product.
(ii) Stability: Shelf life.
(iii) Safety assessment: Documentation of safety based on experience or/and; Toxicology studies.
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(iv) Assessment of efficacy: Documented evidence of traditional use or/and; Activity determination (animals, human).

Why herbal medicine?

Herbal medicines are being used by about 80% of the world population primarily in the developing countries for primary health care. They have stood the test of time for their safety, efficacy, cultural acceptability and lesser side effects. The chemical constituents present in them are a part of the physiological functions of living flora and hence they are believed to have better compatibility with the human body. Ancient literature also mention herbal medicines for age-related diseases viz., memory loss, osteoporosis, diabetic wounds, immune and liver disorders, etc. for which no modern medicine or only palliative therapy is available. These drugs are made from renewable resources of raw materials by eco-friendly processes and will bring economic prosperity to the masses growing these raw materials (Kamboj, 2000).

1.2.1 Global Status of Herbal Medicine

Herbal medicine is still the mainstay of about 75–80% of the world population, mainly in the developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and lesser side effects. However, the last few years have seen a major increase in their use in the developed world. In Germany and France, many herbs and herbal extracts are used as prescription drugs and their sales in the countries of European Union were around $6 billion in 1991 and may be over $20 billion now.

With the US Food & Drug Administration (FDA) relaxing guidelines for the sale of herbal supplement (Gottlieb, 2000), the market is booming with herbal products (Brevoort, 1998). In USA, herbal drugs are currently sold in health food stores with a turnover of about $4 billion in 1996 which is anticipated to double by the turn of the century (Rawls, 1996). As per World Bank reports trade in medicinal plants, botanical drug products and raw material is growing at an annual growth rate between 5 to 15%.

The Global pharmaceutical market has risen from US $550 billion in 2004 worth to a close to US$900 billion in the year 2012. The herbal industry shares about US$62 billion with good growth potential. In India, the herbal drug market is about $ one billion and
the export of plant-based crude drugs is around $80 million. Herbal medicines also find market as nutraceuticals (health foods) whose current market is estimated at about $80–250 billion in USA and also in Europe.

In India the value of botanicals related trade is about US$10 billion per annum with annual export of US$1.1 billion while China annual herbal drugs production is worth US$48 billion with export of US$3.6 billion (Kamboj, 2000).

Presently the United States is the largest market for Indian botanical products accounting for about 50% of the total exports. Japan, Hong Kong, Korea and Singapore are the major importer of the herbal drugs making 66% share of China botanical drug export. Within the European community botanical medicine represents an important share of the pharmaceutical market.

Out of many best 10 popular selling herbal medicines in USA are shown in Table 1.2.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Botanical Name</th>
<th>Market rank as per sale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinacea</td>
<td><em>Echinacea species</em></td>
<td>1</td>
</tr>
<tr>
<td>Garlic</td>
<td><em>Allium sativum</em></td>
<td>2</td>
</tr>
<tr>
<td>Goldenseal</td>
<td><em>Hydratis Canadensis</em></td>
<td>3</td>
</tr>
<tr>
<td>Inseng</td>
<td><em>Panax species</em></td>
<td>4</td>
</tr>
<tr>
<td>Ginko</td>
<td><em>Ginko biloba</em></td>
<td>5</td>
</tr>
<tr>
<td>Saw Palmeto</td>
<td><em>Serenoa repens</em></td>
<td>6</td>
</tr>
<tr>
<td>Aloe vera</td>
<td><em>Aloe barbadensis</em></td>
<td>7</td>
</tr>
<tr>
<td>Ephedra</td>
<td><em>Ephedra species</em></td>
<td>8</td>
</tr>
<tr>
<td>Eleuthero</td>
<td><em>Eleutherococcus senticosus</em></td>
<td>9</td>
</tr>
<tr>
<td>Cranberry</td>
<td><em>Vaccinium macrocarpon</em></td>
<td>10</td>
</tr>
</tbody>
</table>

1.2.2 Indian Herbal Trade in World Scenario

The utilization of herbal drugs is on the flow and the market is growing step by step (Kamboj, 2000). The annual turnover of the Indian herbal medicinal industry is about Rs. 2,300 crore as against the pharmaceutical industry’s turnover of Rs. 14,500 crores with a growth rate of 15 percent (Krishnan, 1998). The export of medicinal plants and herbs...
from India has been quite substantial in the last few years. India is the second largest producer of castor seeds in the world, producing about 1,25,000 tonnes per annum. The major pharmaceuticals exported from India in the recent years are isabgol, opium, alkaloids, senna derivatives, vinca extract, cinchona alkaloids, ipecac root alkaloids, solasodine, Diosgenine/16DPA, Menthol, gudmar herb, mehdi leaves, papian, rauwolfia guar gum, Jasmine oil, agar wood oil, sandal wood oil, etc (Kokate et al, 2005). The turnover of herbal medicines in India as over-the-counter products, ethical and classical formulations and home remedies of traditional systems of medicine is about $ one billion and export of herbal crude extract is about $ 80 million. The herbal drug market in India is about $1 billion.

To sustain in the global market of herbal medicines and to gain entry into developed countries India follows the basic requirements which includes:

(i) well-documented traditional use,
(ii) single-plant medicines,
(iii) medicinal plants free from pesticides, heavy metals etc.,
(iv) standardization based on chemical and activity profile, and
(v) Safety and stability.

However, mode of action studies in animals and efficacy in human will also be supportive. Such scientifically generated data will project herbal medicine in a proper perspective and help in sustained global market.

1.2.3 Research Approach to Herbal Products

The path of Reverse Pharmacology, arising from observational therapeutics is complementary to other approaches for natural drug development (Fig. 1.1).
The diversity of medical uses of plant is at times daunting for a new entrant to the field. But for a multidisciplinary research and a development network the options of research approach provide deep motivation for identification of new pharmacophores. Besides expanding the herbal therapeutic and preventive armamentarium, new pharmacophores may help to evolve new targets of drug action as well as a possibility for combinatorial chemistry on the novel pharmacophores. For example, curcumin has been a target molecule for a significant endeavour for a large number of combinatorial compounds. The Council of Scientific and Industrial Research (CSIR), in India has initiated sizeable and meaningful efforts for the development of herbal-based formulations for diabetes, arthritis and hepatitis by a national network programme (Patwardhan et. al, 2004). The industry, the academia and the government research laboratories work in close collaboration. Interesting and novel activities have been detected with the selected plants and some of the active ingredients of therapeutically demonstrable effects e.g. glycaemic control and inhibition of HbA1c (glycosylated haemoglobin) level coupled with a reduction in in vitro formation of Amadori products. The diverse approaches to herbal drugs have led to interesting hits and novel activities, which need further in depth drug development efforts, both as herbal as well as new single molecule drugs.