Chapter 1

Introduction
Cancer on a brief:

Cancer is a class of diseases characterized by out of control cell growth. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected (Lakshmi et al., 2011).

Cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called tumors (except in the case of leukemia where cancer prohibits normal blood function by abnormal cell division in the blood stream). Tumors can grow and interfere with the digestive, nervous, circulatory systems and they can release hormones that alter body function. Tumors that stay in one spot and demonstrate limited growth are generally considered to be benign. More dangerous, or malignant, tumors form when two things occur:

1. a cancerous cell manages to move throughout the body using the blood or lymph systems, destroying healthy tissue in a process called invasion.

2. that cell manages to divide and grow, making new blood vessels to feed itself in a process called angiogenesis.

When a tumor successfully spreads to other parts of the body and grows, invading and destroying other healthy tissues, it is said to have metastasized. This process itself is called metastasis, and the result is a serious condition that is very difficult to treat.

Cancer may spread due to their adhesion (stickiness) properties. Certain molecular interactions between cells and the scaffolding that holds them in place (extracellular matrix) cause them to become unstuck at the original tumor site; they become dislodged, move on and then reattach themselves at a new site (Reticker-Flynn et al., 2012).

The researchers say this discovery is important because cancer mortality is mainly due to metastatic tumors, those that grow from cells that have travelled from their original site to another part of the body. Only 10% of cancer deaths are caused by the primary tumors.
The scientists, from the Massachusetts Institute of Technology (MIT), say that finding a way to stop cancer cells from sticking to new sites could interfere with metastatic disease, and halt the growth of secondary tumors. In 2007, cancer claimed the lives of about 7.6 million people in the world.

One of the most important factors in classifying a tumor as benign or malignant is its invasive potential. If a tumor lacks the ability to invade adjacent tissues or spread to distant sites by metastasizing then it is benign, whereas invasive or metastatic tumours are malignant (Atkins et al., 2006). For this reason, benign tumours are not classed as cancer (Silverstein et al., 2006). Benign tumours will grow in a contained area usually encapsulated in a fibrous connective tissue capsule. The growth rates of benign and malignant tumors also differ; benign tumors generally grow more slowly than malignant tumors. Although benign tumors pose a lower health risk than malignant tumors, they can both be life-threatening in certain situations. There are many general characteristics which apply to either benign or malignant tumors, but sometimes one type may show characteristics of the other. For example, benign tumors are mostly well differentiated and malignant tumors are often undifferentiated. However, undifferentiated benign tumors and differentiated malignant tumors can occur (Skoric et al., 1999; Song et al., 2012). Although benign tumors generally grow slowly; cases of fast growing benign tumors have also been documented (Sagel and Ablow, 1968). Some malignant tumors are mostly non-metastatic such as in the case of basal cell carcinoma (Strayer et al., 2008).

Cancer is a deadly disease, responsible for 2-3% deaths worldwide annually. A new report on the global cancer burden provides data on and insights into cancer incidence and mortality worldwide. Global Cancer Facts & Figures, 3rd Edition, produced by the American Cancer Society in partnership with the International Agency for Research on Cancer (IARC), was
released February 4, 2015 on World Cancer Day - bringing attention to the growing cancer epidemic and what can be done to address it.

About 14.1 million new cancer cases were diagnosed in 2012 worldwide. More than half of these (8 million) occurred in economically developing countries. Among them 8.2 million were died in 2012 worldwide. It is expected that about 21.7 million new cancer cases will be diagnosed in 2030. And, by 2030, 13 million cancer deaths are predicted. However, these projections only reflect population growth and aging, so these figures will likely be much larger “due to the adoption of lifestyles that are known to increase cancer risk, such as smoking, poor diet, physical inactivity, and fewer pregnancies, in economically developing countries” (Global cancer facts; ACS 2015).

The current Indian population is 1,270,272,105 (1.27 billion). The incidence of cancer in India is 70-90 per 100,000 populations. And cancer prevalence is established to be around 2,500,000 (2.5 million) with over 800,000 new cases and 5,50,000 deaths occurring each year. More than 70% of the cases present in advanced stage accounting for poor survival and high mortality. About 6% of all deaths in India are due to cancers which contribute to 8% of global cancer mortality (Bushan, 2014).

In recent times there has been increase in incidence of cancer in India as nearly two people are diagnosed every minute with cancer. This is mainly attributed to urbanisation, industrialisation, life style changes, population growth and increase in life span. In India, life expectancy at birth has risen from 45 years in 1971 to 62 years in 1991 to 71 years expected by 2021-2025 and so has the risk to harbour cancer (Global Cancer, 2015).

The predominant risk factors associated with cancers are genetic, environmental and life style factors which include tobacco, alcohol, infections (HIV, HPV, HBV, HCV, H. Pylori) and dietary factors which overall are involved in 80-90% cases. Tobacco contributes directly to about 50% of cancers in males and 10-15% cancers in females. Most of the cancers have
some relationship with diet. Predominant among them are cancer of esophagus, stomach, colon & liver. Consumption of large amounts of red chillies, food at very high temperatures and alcohol consumption are the main risk factors for stomach cancers in India (Cancer: Facts, 2014).

Difference between normal and cancer cell division

Cancer symptoms are quite varied and depend on where the cancer is located, where it has spread, and how big the tumor is. Some cancers can be felt or seen through the skin - a lump on the breast or testicle can be an indicator of cancer in those locations. Skin cancer (melanoma) is often noted by a change in a wart or mole on the skin. Some oral cancers present white patches inside the mouth or white spots on the tongue (Barber et al., 2012).

Other cancers have symptoms that are less physically apparent. Some brain tumors tend to present symptoms early in the disease as they affect important cognitive functions. Pancreas cancers are usually too small to cause symptoms until they cause pain by pushing against nearby nerves or interfere with liver function to cause a yellowing of the skin and eyes called
jaundice. Symptoms also can be created as a tumor grows and pushes against organs and blood vessels. For example, colon cancers lead to symptoms such as constipation, diarrhoea, and changes in stool size. Bladder or prostate cancers cause changes in bladder function such as more frequent or infrequent urination.

As cancer cells use the body's energy and interfere with normal hormone function, it is possible to present symptoms such as fever, fatigue, excessive sweating, anaemia, and unexplained weight loss. However, these symptoms are common in several other maladies as well. For example, coughing and hoarseness can point to lung or throat cancer as well as several other conditions (Chakraborty R).

When cancer spreads, or metastasizes, additional symptoms can present themselves in the newly affected area. Swollen or enlarged lymph nodes are common and likely to be present early. If cancer spreads to the brain, patients may experience vertigo, headaches, or seizures. Spreading to the lungs may cause coughing and shortness of breath. In addition, the liver may become enlarged and cause jaundice and bones can become painful, brittle, and break easily. Symptoms of metastasis ultimately depend on the location to which the cancer has spread.

There are five broad groups that are used to classify cancer.

1. Carcinomas are characterized by cells that cover internal and external parts of the body such as lung, breast, and colon cancer.

2. Sarcomas are characterized by cells that are located in bone, cartilage, fat, connective tissue, muscle, and other supportive tissues.

3. Lymphomas are cancers that begin in the lymph nodes and immune system tissues.

4. Leukemias are cancers that begin in the bone marrow and often accumulate in the bloodstream.

5. Adenomas are cancers that arise in the thyroid, the pituitary gland, the adrenal gland, and other glandular tissues.
Cancers are often referred to by terms that contain a prefix related to the cell type in which the cancer originated and a suffix such as -sarcoma, -carcinoma, or just -oma. Common prefixes include:

- Adeno- = gland
- Chondro- = cartilage
- Erythro- = red blood cell
- Hemangio- = blood vessels
- Hepato- = liver
- Lipo- = fat
- Lympho- = white blood cell
- Melano- = pigment cell
- Myelo- = bone marrow
- Myo- = muscle
- Osteo- = bone
- Uro- = bladder
- Retino- = eye
- Neuro- = brain

**How is cancer diagnosed and staged?**

Early detection of cancer can greatly improve the odds of successful treatment and survival. Physicians use information from symptoms and several other procedures to diagnose cancer. Imaging techniques such as X-rays, CT scans, MRI scans, PET scans, and ultrasound scans are used regularly in order to detect where a tumor is located and what organs may be affected by it. Doctors may also conduct an endoscopy, which is a procedure that uses a thin tube with a camera and light at one end, to look for abnormalities inside the body.
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Extracting cancer cells and looking at them under a microscope is the only absolute way to diagnose cancer. This procedure is called a biopsy. Other types of molecular diagnostic tests are frequently employed as well. Physicians will analyze your body's sugars, fats, proteins, and DNA at the molecular level. For example, cancerous prostate cells release a higher level of a chemical called PSA (prostate-specific antigen) into the bloodstream that can be detected by a blood test. Molecular diagnostics, biopsies, and imaging techniques are all used together to diagnose cancer (Chakraborty R).

After a diagnosis is made, doctors find out how far the cancer has spread and determine the stage of the cancer. The stage determines which choices will be available for treatment and informs prognoses. The most common cancer staging method is called the TNM system. T (1-4) indicates the size and direct extent of the primary tumor, N (0-3) indicates the degree to which the cancer has spread to nearby lymph nodes, and M (0-1) indicates whether the cancer has metastasized to other organs in the body. A small tumor that has not spread to lymph nodes or distant organs may be staged as (T1, N0, M0), for example (Cancer: Symptoms, 2015).

TNM descriptions then lead to a simpler categorization of stages, from 0 to 4, where lower numbers indicate that the cancer has spread less. While most Stage 1 tumors are curable, most Stage 4 tumors are inoperable or untreatable.

Cancer treatment depends on the type of cancer, the stage of the cancer (how much it has spread), age, health status, and additional personal characteristics. There is no single treatment for cancer, and patients often receive a combination of therapies and palliative care. Treatments usually fall into one of the following categories: surgery, radiation, chemotherapy, immunotherapy, hormone therapy or gene therapy.

Cancers that are closely linked to certain behaviors are the easiest to prevent. For example, choosing not to smoke tobacco or drink alcohol significantly lower the risk of several types
of cancer - most notably lung, throat, mouth, and liver cancer. Even if you are a current
tobacco user, quitting can still greatly reduce your chances of getting cancer.
Skin cancer can be prevented by staying in the shade, protecting yourself with a hat and shirt
when in the sun, and using sunscreen. Diet is also an important part of cancer prevention
since what we eat has been linked to the disease. Physicians recommend diets that are low in
fat and rich in fresh fruits and vegetables and whole grains.
Certain vaccinations have been associated with the prevention of some cancers. For example,
many women receive a vaccination for the human papilloma virus because of the virus's
relationship with cervical cancer. Hepatitis B vaccines prevent the hepatitis B virus, which
can cause liver cancer.
Some cancer prevention is based on systematic screening in order to detect small
irregularities or tumors as early as possible even if there are no clear symptoms present.
Breast self examination, mammograms, testicular self examination, and Pap smears are
common screening methods for various cancers (Cancer: Symptoms, 2015).
Researchers from North-western University Feinberg School of Medicine in Chicago
reported in the journal Circulation that the 7 steps recommended for protection against heart
disease can also reduce the risk of developing cancer. They include being physically active,
eating a healthy diet, controlling cholesterol, managing blood pressure, reducing blood sugar
and not smoking (Paddock, 2013).

**Targeting cancers for new drug therapies**

Researchers at The Institute of Cancer Research reported in the journal Nature Reviews Drug
Discovery (January 2013 issue) that they have found a new way of rapidly prioritizing the
best drug gable targets online. They managed to identify 46 previously overlooked targets.
The researchers used the canSAR database together with a tool and were able to compare up
to 500 drug targets in a matter of minutes. With this method, it is possible to analyze huge
volumes of data to discover new drug targets, which can lead to the development of effective cancer medications.

The scientists analyzed 479 cancer genes to determine which ones were potential targets for medications. Their approach was effective - they found 46 new potentially “druggable” cancer proteins. Not only will this approach lead to much more targeted cancer drugs, but also considerably cheaper ones, the authors added (Cancer: Treatments, 2015).

**Traditional Plant Based Medicines: Past to Present**

Herbal products have gained increasing popularity in the last decade, and are now used by approximately 20% of the population. Herbal products are complex mixtures of organic chemicals that may come from any raw or processed part of a plant, including leaves, stems, flowers, roots, and seeds. The resulting products contain dozens of chemicals, including fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, and others. Because any given herb contains multiple ingredients, some manufacturers attempt to create standardized herbal products by identifying a suspected active ingredient and altering the manufacturing process to obtain a consistent amount of this chemical (Bent, 2008). Under the current law, herbs are defined as dietary supplements, and manufacturers can therefore produce, sell, and market herbs without first demonstrating safety and efficacy, as is required for pharmaceutical drugs. Although herbs are often perceived as “natural” and therefore safe, many different side effects have been reported owing to active ingredients, contaminants, or interactions with drugs.

Nature has evolved over time to produce a bewildering diversity of secondary metabolites. Based on empirical observations and folklore, natural product extracts were the first, and for a long time, the only medicines available to mankind (Ganesan, 2008). The medicinal use of natural products compounds that are derived from natural sources such as plants, animals or micro-organisms precedes recorded human history probably by thousands of years.
Palaeoanthropological studies at the cave site of Shanidar, located in the Zagros Mountains of Kurdistan in Iraq, have suggested that more than 60,000 years ago, Neanderthals might have been aware of the medicinal properties of various plants, as evidenced by pollen deposits in one of the graves at the site. Over the ensuing millennia, humankind discovered and made use of an enormous range of natural compounds; the latest version of the Dictionary of Natural Products (DNP; http://dnp.chemnetbase.com) has just over 214,000 entries (Solecki, 1975).

Throughout our evolution, the importance of natural products for medicine and health has been enormous. Since our earliest ancestors chewed on certain herbs to relieve pain, or wrapped leaves around wounds to improve healing, natural products have often been the sole means to treat diseases and injuries. In fact, it has only been during the past decades that natural products have taken a secondary role in drug discovery and drug development, after the advent of molecular biology and combinatorial chemistry made possible the rational design of chemical compounds to target specific molecules. The past few years, however, have seen a renewed interest in the use of natural compounds and, more importantly, their role as a basis for drug development. The modern tools of chemistry and biology in particular, the various ‘-omics’ technologies now allow scientists to detail the exact nature of the biological effects of natural compounds on the human body, as well as to uncover possible synergies, which holds much promise for the development of new therapies against many devastating diseases, including dementia and cancer (Ji et al., 2009).

Owing to the diverse biological activities and medicinal potentials of natural products, nearly every civilization has accumulated experience and knowledge of their use. The oldest medical text comes from ancient Mesopotamia, circa 2600 BC, and is written on hundreds of clay tablets in cuneiform. It describes approximately 1,000 plants and plant-derived substances, such as the oils of Cedrus species (cedar), the resin of Commiphora myrrha (myrrh) and the juice of the poppy seed Papaver somniferum (Newman et al., 2000). Many of
these herbs and formulations are still used today. The ancient Egyptian Ebers Papyrus, dating from around 1550 BC, contains about 800 complex prescriptions and more than 700 natural agents such as Aloe vera (aloe), Boswellia carteri (frankincense) and the oil of Ricinus communis (castor) (Zhong & Wan, 1999). The famous Greek physician, Hippocrates of Cos (circa 460-377 BC), collected more than 400 natural agents and described their use in his Corpus Hippocraticum. He mentioned using melon juice as a laxative, described the diuretic effect of the juice from Ornithogalum caudatum (squill) and detailed how to use an extract from Atropa belladonna as an anaesthetic. He also advised using an extract of Veratrum album (white hellebore) as anemetic and how to use olive oil to improve wound healing (Castiglioni, 1985). Roman physicians built on this extensive knowledge and added their own insights and experience. Pedanius Dioscorides (circa 40-90 AD) compiled De Materia Medica, which described the dosage and efficacy of about 600 plant-derived medicines and laid the foundations of pharmacology in Europe (Wermuth, 2003). Galen (129-200 AD), another famous Greek physician and pharmacist, recorded 540 plant-derived medicines and demonstrated that herbal extracts contain not only beneficial components, but also harmful ingredients (Cai, 1992; Cheng & Zhen, 2004).

Natural product-based medicines also flourished in the Orient. Charaka Samhita, the first treatise devoted to the concepts and practice of Indian Ayurveda, was written around 900 BC and contains 341 plant derived medicines. The Sushruta Samhita (circa 600 BC) was mainly devoted to surgical practices, but also described 395 medicinal plants and 57 animal-derived products (Dev, 1999). Traditional Chinese medicine (TCM) is also famous for its extensive use of natural products. The most primitive Chinese medicinal book, Wu Shi Er Bing Fang—which translates to Prescriptions for Fifty Two Diseases—was compiled around 350 BC and lists 247 natural agents and about 150 combinatorial drug formulae, along with practical
advice regarding the properties, efficacies and synergies of natural medicines (Wan & Zhong, 1990; Jiao & Wang, 2005).

The natural products derived from medicinal plants have proven to be an abundant source of biologically active compounds, many of which have been the basis for the development of new lead chemicals for pharmaceuticals. With respect to diseases caused by microorganisms, the increasing resistance in many common pathogens to currently used therapeutic agents, such as antibiotics and antiviral agents, has led to renewed interest in the discovery of novel anti-infective compounds. As there are approximately 500,000 plant species occurring worldwide, of which only 1% has been phytochemically investigated, there is great potential for discovering novel bioactive compounds (Palombo, 2011).

It has been claimed that the vast majority of the world’s natural compounds have not been tested for biological activity and that several novel sources of biodiversity are potentially available. These include a broader range of plant species than traditionally sampled, marine organisms and microbial diversity. Other unexplored sources of natural products (particularly foodstuffs and drinks) that could be searched for drug leads have been highlighted more recently. However, it has also been pointed out that, because identical or similar compounds can be found in several species from different geographical locations, a broad sampling of biodiversity may not be essential for successful natural product-based drug discovery (Harvey, 2007). In the period 1970-2006, a total of 24 unique natural products were discovered that led to an approved drug.

These naturally produced chemicals are part of our food and till now have formed the basis of our medicine. Infectious diseases were the greatest threat to the mankind for most of our existence. Discoveries of several small molecules (many of them synthesized by living organisms, e.g., penicillin and streptomycin) and vaccines in the early part of the 20th century started a chain of events culminating in control of many of these diseases (Mondal et al.,
Today we are facing a new epidemic of lifestyle diseases of which cancer is a major one. Could the natural products come to our rescue again? Already many natural products or natural product derived molecules form a major part of our arsenal against cancer. The examples include, Taxanes, Vinca alkaloids, podophyllotoxins and camptothecin. Could we find many more?

In these regards literature survey revealed many plants which are traditionally used for the several diseases related to cancer. Among these *Zanthoxylum alatum* Roxb. (Rutaceae) has been selected on the basis of literature review for the studies in Phytotherapy and Pharmacology research laboratory, Department of Pharmaceutical Technology, Jadavpur University.

*Zanthoxylum alatum* (Syn: *Zanthoxylum armatum*) Roxb. (Family: Rutaceae) is an evergreen plant of the Himalayan regions in India, commonly known as Tejphal (Hindi) and Timur (Nepali) (Singh & Singh, 2011; Tiwary *et al.*, 2007). The ethnomedicinal importance of its seeds has been well known for a long time in Indian medical system as a stomachic, carminative, disinfectant, and antiseptic; and for the treatment of fever, dyspepsia, cholera, anthelmintic, general debility, and preventing snake bites (Jain *et al.*, 2001; Kalia *et al.*, 1999;
Prakash et al., 2012). Nepalese traditionally used the fruit decoction in abdominal pain; bark extract for cholera, diabetes, and asthma. Pickles from the fruits are used by Nepalese for treating colds and coughs, tonsillitis, headache, fever, and high-altitude sickness (Geweli & Awale, 2008). Scientific bioactivity determination studies have revealed its larvicidal (Tiwary et al., 2007), hepatoprotective, antioxidant (Ranawat et al., 2010), antinociceptive, antiinflammatory, and antipyretic activities (Guo et al., 2011). Various phytopharmaceuticals, such as berberine, dictamnine, xanthoplanine, armatamid, asarinin, fargesin, α- and β-amyris and lupeol are present in the plant (Kalia et al., 1999; Nadkarni, 2002). The present study evaluates the apoptotic activity of the methanol extract of Z. alatum leaves through bcl-2/bax pathway and other supportive parameters.
References


