Introduction
INTRODUCTION

Cancer is an insidious disease which develops from DNA mutations that alter crucial pathways that normally regulate tissue homeostasis, cell survival and/or cell death. [Can-Cer / Kan’Ser] cancer a neoplastic disease the natural cause of which is fatal. (Dorland’s, 2007). Cancer is not just one disease, but a large group of almost 100 diseases. The two main characteristics of Cancer are uncontrolled growth of the cells in the human body and the ability of those cells to migrate from the original site and spread to distant sites, thus exhibiting the properties of invasion, metastasis and are highly anaplastic. It causes changes in the genetic material of the cells, via deoxyribonucleic acid [DNA].

The altered cells pass on inappropriate genetic information to their progeny cells and begin to proliferate in an abnormal and destructive way. In Cancer, cell growth is unregulated. As the Cancer cells continue to proliferate, the mass of abnormal tissues that they form enlarges, ulcerates and begins to shed cells that spread the disease locally or to distant site. This migration is called metastasis. Not all tumors are invasive. Some are benign and do not spread to other parts of the body, these are rarely life – threatening.

The International Agency for Research on Cancer provided the most accurate assessment of Global Cancer @ 2008, those 12.7 million new cases of Cancer 7.6 million Cancer deaths worldwide in 2012; Cancer Research UR has estimated 14.1 million new cases of Cancer, with incidence rate varying across the world. There were 8.2 million deaths from Cancer in the world in 2012 [Cancer Research., 2013].

Early diagnosis of cancer can highly improve the treatment and survival like the examination of tissues biopsy specimen by a pathologist, imaging techniques such as X rays, CT Scans, MRI
Scans, PET Scans & Ultra Sound Scans are used to detect the location of the tumor. Based on the diagnosis cancer could be treated with various therapies like Chemotherapy, Radio Therapy, Immuno Therapy and so on. A substance or agent that causes the development or increases the incidence of cancer is known as Carcinogen. The process of initiating and promoting cancer is known as Carcinogenesis. Tobacco, Smoke, Radiation, Infectious agents or chemicals are few examples for Carcinogens.

**Cancer Classification**

Cancers are classified by the type of cells that resembles the tumor and therefore the tissue is presumed to be the origin of the tumor.

**Carcinoma:** These are the cancers that arise in the epithelium. Carcinomas can be subdivided into two categories as Adenomas and Squamous Cell Carcinoma

- **Adenocarcinoma**’s are cancers that develop in an organ or a gland
- **Squamous Cell Carcinoma**’s refers to the cancer’s that originate in the skin.

**Sarcoma:** They are cancers originating from supportive and connective tissues of the body such as bone, cartilage muscle, tender bones and fat. Sarcoma tumors usually resemble the tissue in which they grow.

**Leukemia:** [Liquid Cancer]

Leukemia’s are cancers of the bone marrow. The word Leukemia means “White Blood” in Greek. The disease is often associated with over production of immature white blood cells. Leukemia also affects red blood cells and cause blood clotting.
Lymphoma [Solid Cancer]

Lymphomia’s develop in the nodes or glands of lymphatic system that purify fluids and produce infection – fighting white blood cells. Unlike leukemia, lymphomas are “Solid Cancers”. [National Institute of Health] Germ Cell Tumor: Tumors derived from totipotent cells.

Gliomas: They are cancers of the nerve tissues.

Myeloma: Myeloma is cancer that originates in the plasma cells of the bone marrow.

Cancers are often referred by terms that contrary a prefix related to the cell type in which the Cancer originated and suffix such as – Sarcoma, Carcinoma or just Oma.

Example

Erythro – Red blood cells

Adeno – Gland

Myo – Muscle

Hepato – Liver

Melano – Pigment Cell

Osteo – Bone

Changes occurring during cancer

- Evading immune destruction: Cancer cells evade destruction by lymphocytes, macrophages and natural killer cells.
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- Evading growth suppressors: In order to continue growing, cancer cells must circumvent normal growth signaling.
- Reprogramming energy metabolism: Cancer cells acquire the capability to modify or reprogram, cellular metabolic pathways to support increased cell proliferation.
- Sustaining proliferative signaling: Cancer cells dysregulate normal growth signaling to sustain ongoing proliferation.
- Enabling replicative immortality: Cancer cells over express telomerase in order to replicate indefinitely.
- Genome instability and mutation: Cancer cells take advantage of successive mutations in order to foster tumorigenesis.
- Activation Invasion and Metastasis: The process of invasion and metastasis involves a series of steps ending in colonization of foreign tissue.
- Tumor promoting inflammation: Inflammation provides the micro-environment with factors that may aid in tumor growth.
- Inducing Angiogenesis: The formation of new blood vessels is critical for sustained tumor growth and metastasis.
- Resisting cell death: Tumor cells evade apoptosis (Programmed cell death) by dysregulating apoptotic pathways (Ghobrial et al., 2005).

Carcinogenesis

Cancer is of genetic origin. Due to the imbalance in the genes responsible for tumor induction (proto oncogenes) or tumor suppressor genes it disrupt the cell cycle and result in uncontrolled proliferation, invasion, differentiation and loss of function and metastasis.
It is not all mutations which are caused by mutagens in a cell may lead to the induction of cancer. Only when the accumulated mutations get coupled with promoters, it will have the potency to convert a normal cell to a cancerous cell. Recent reports have indicated that the disruption of circadian rhythm is also associated with cancers both clinically and experimentally (Mormont and Levi., 1997 and Canaple et al., 2003).

**Various Approaches in Cancer Treatment**

**Conventional methods**

Surgery, radiotherapy and chemotherapy are the conventional methods to treat cancer.

**Newer approaches:** several newer approaches/drugs have originated which comprises of chemoprevention (synthetic and natural agents), drugs promoting differentiation, antimetastatic drugs, anti angiogenic drugs, hypoxic tumor cell specific agents, anti telomerase drugs, aromatase inhibitors, biological response modifiers, radiosensetizers, antisense therapy, gene therapy and cancer vaccines etc have emerged. Other steps of treatment like reduction of side effects of anticancer agents using 5 – HT3 receptor antagonists, interferons and interleukins are also used.

**Liver**

The Liver is the largest organ in the body. **Figure 1** shows the Structure of liver. It weighs about 1.5 kg in the average adult human. It lies under the right ribs just beneath the right lung. It is reddish – brown in color. It is shaped like a pyramid and divided into right and left lobes (Gyton C, 7th ED).
Functions of liver (Figure 2)

- Liver function as a Blood Reservoir.
- Liver possess Regeneration property.
- It plays a vital role in the process of digestion through the production of bile.
- Hepatocytes absorbs glucose and store it as glycogen.
- Hepatocytes of the liver monitor the contents of the blood and remove many toxic substances before they get circulated to the other parts of the body.
- Liver is the major site for metabolism of the carbohydrates, proteins & lipids.
- Liver stores many essential nutrients, vitamins and minerals obtained from blood passing through the hepatic portal system.
- It maintains the homeostasis of the blood glucose.
- It is responsible for the production of clotting factors namely, prothrombin, fibrinogen and albumin.
- Liver functions as an organ of immune system through the function of Kupffer cells.
- Kupffer cells play an important role as macrophages by capturing & digesting the bacteria, fungi, parasites, worn out blood cells and cellular debris. [Hepatology text book & Atlas, 2008]

Types of Liver Tumors

- The Liver is made up of several different types of cells. So several types of tumors can form.
  - Non cancers tumors – Benign
  - Cancerous Tumors – Malignant, Can spread to other parts of the body
Figure 1 Structure of Liver

![Liver structure diagram]

Figure 2 Functions of Liver

Liver Functions:
- Removes potentially toxic byproducts of certain medications.
- Prevents shortages of nutrients by storing vitamins, minerals, and sugar.
- Metabolizes, or breaks down, nutrients from food to produce energy when needed.
- Produces most proteins needed by the body.
- Helps your body fight infection by removing bacteria from the blood.
- Produces most of the substances that regulate blood clotting.
- Produces bile, a compound needed to digest fat and to absorb vitamins A, D, E, and K.
Common Benign Tumors of Liver

Benign tumors sometimes grow large enough to cause problem but they do not grow into nearby tissues or spread to distant parts of the body. They can be treated by surgery.

- Hemangioma: Liver Hemangiomas are non-cancerous and do not cause cancer to develop. It grows to about 4 cm in size. It is an abnormal growth of blood vessels of the Liver that begins in the fetus. Some Hemangiomas may rarely enlarge and bleed which may require surgical removal.
- Hepatic Adenomas: Hepatic Adenoma is a benign tumor that starts from Hepatocytes. Hepatic Adenoma may grow in women who take hormone pills. In most cases there are symptoms like pain or a mass in the abdomen (stomach area) or blood loss. There is a risk that the tumor could rupture.
- Focal Nodular Hyperplasia [FNH] – It is a tumor like growth of several cell types [Hepatocytes, Bile duct cells, Connective tissue cells]. It is asymptomatic, rarely grows or bleeds and has no malignant potential. [Li Chun Hsee et al., 2005]

Malignant, implies that the lesion can invade and destroy adjacent structures and spread to distant site [Metastasize] to cause death [Robbins Basic Pathology]

Pre – Malignancy, pre cancer or noninvasive tumor – A neoplasm that does invade but has potential to progress to cancer if left untreated.

Liver Cancer Predominance

In United States about 3000 people die each year from HCC or Chronic liver disease caused by HBV infection [CDC, 2008a]. In American Population there was high providence of
chronic HBV infection and high risk of HCC [Chang et al., 2007]. Vong and Bell, 2004 stated that American Indian and Alaska Native people were found to have highest liver related death rate in United States.

Hepatocellular Carcinoma (HCC) is the fifth most common tumor and third leading cause of global cancer related mortality. Chronic HBV and HCV infections could lead to HCC, which is a major type of liver cancer (But et al., 2008; Mc Mohan., 2004, Tan et al., 2008). The advancement in the early diagnosis and the improvement in the treatment including new targeted therapy were found to improve greatly the prognosis of HCC patients. Hepato Cellular Carcinoma (HCC) is the most common type of primary liver cancer representing 85% of liver cancers. Apart from HCC, liver cancer includes cholangio carcinoma originating in the cells that line the bile duct, angio sarcoma which starts in the blood vessels of the liver and hepatoblastoma which is very rare and usually affects young children [Monica Harra et al., 2011].

Predominance of HCC

HCC is the fastest growing cause of cancer related death, with the annual range of HCC increasing from 1.3/100,000 during 1978 – 1980 to more than 5.0/100,000 in 2007. In all population, men have a higher incidence of HCC than women, with an average man to woman ratio of 2:1 and even higher ratio in highly endemic areas. Generally HCC is uncommon in the first 3-4 decades of life and increases progressively thereafter with peak incidence in the 7th and 8th decades.

HCC accounts for up to 75% to 85% of primary liver cancer in the United States (US) (Mc Glyn et al., 2001) and for over 90% in high risk areas. People in developing countries, such
as Sub-Saharan, Africa, China, Taiwan, Korea, Vietnam were found to be predominantly affected by HCC (Bosch et al., 2004, Larson 2005).

The incidence has been increasing in recent years in the Mediterranean countries, where as in Italy, the incidence and mortality rates are at a median frequency compared to other populations. It was the seventh cause of death for tumor with about 5000 deaths per year (Levi et al., 2007, Montalto et al., 2002, La Vecchia et al., 2002).

Muto et al., 1996 stated that Hepatocellular carcinoma is one of the most common malignancies in the world, especially in Asia and Africa (Figure 3). The majority of patients are found to possess pre-existing cirrhosis at the time they develop hepatocellular carcinoma. Apart from many treatments for this disease in recent decades, its long – term therapeutic outcome remained very poor. Prevention seemed to be the best strategy in lowering the present incidence of the disease (Muto et al., 1996, Muto et al., 1998).

**Risk factors**

Cirrhosis

Hepatitis B virus

Hepatitis C virus

Alcohol consumption

Family history

Vinyl chloride exposure

Cigarette smoking
Figure 3  Predominance of HCC worldwide
Diabetes mellitus

Hypothyroidism

Obesity

Aflatoxin exposure

The two major risk factors for HCC are chronic HBV and HCV infections. It was estimated that 78% of HCC cases and 57% of liver cirrhosis cases are caused by chronic HBV and HCV infections (Perz et al., 2006). Population with Liver cirrhosis has the highest risk of developing HCC (Forner et al., 2012). Cirrhosis may be due to HCV or HBV infection.

The commonest cause of HCC worldwide was found as chronic hepatitis B infection and in Europe hepatitis C infection leads to HCC. Both hepatitis C and B, co-infection results in increased risk of HCC (Keith E Stuart and Zsofia K Stadler., 2012).

The major known risk factors for HCC are viral (Chronic hepatitis B and Hepatitis C), Toxic (alcohol and aflatoxins), metabolic (diabetic and non–alcoholic fatty liver diseases, hereditary haemochromatosis), immune related (primary biliary cirrhosis and auto immune hepatitis), food additives, environmental and industrial toxic chemicals, air and water pollutants (Farazil et al., 2006).

In Egypt, between 1993 and 2002, there was almost two – fold increase in HCC amongst chronic liver patients (El – Zayadi et al., 2005). It has been found that hepatitis C Virus (HCV) and Schistosomiasis play a major role in the development of HCC in Egypt where the highest prevelance of HCV in the world which has been attributed to previous public health eradication schemes for Schistosomiasis (Frank et al., 2000, Hassan et al., 2001).
Adami et al., (1996), demonstrated that diabetes mellitus is a major risk factor for hepatocellular carcinoma. In a prospective study of 578,000 individuals it was proved that the risk of HCC incidence is associated with each of the components of the metabolic syndrome [BMI, blood pressure, serum triglycerides and blood glucose]. Starley et al., (2010), identified the potential effect of fatty liver leads to hepatosteatitis which could progress to liver cirrhosis and further alarms as a causal factor in the development of hepatocellular carcinoma.

**Types of HCC**

Cancer staging would serve to select the appropriate primary and adjuvant therapy. (EASL) European Association for the study of Liver, the panel of experts, has proposed diagnostic criteria for HCC (Bruix et al., 2001).

**Classification based on the size of the nodules**

- A nodule <2cm in size has to be diagnosed by means of conventional pathological criteria.
- Accurate fine – needle biopsys are done, based on the nodular size. It ranges about 50% - 70% (Borzio et al., 2003).
- If nodules are <1cm, only half of them will correspond to HCC. Differentiation of early well differentiated HCC from preneoplastic lesions is a histopathologic challenge (Theise et al., 2002; Kojiro, 2004).
- If nodules are >2 cm in liver cirrhosis, HCC may be confidently diagnosed with the help of (ultrasonograph, spiral CT or magnetic resonance imaging) or by a single positive imaging technique associated with alphafetoprotein (AFP) >400 ng/ml (Bruix et al., 2001).
**Early HCC**

In early HCC there might be single tumor with proper liver function (no partial hypertension, normal bilirubin) for resection. It might be single tumors ≤5 cm or three nodules ≤3 cm for liver transplantation, or single tumors ≤3 cm for percutaneous treatments (Llovet et al., 1999a, Liovet et al., 2003).

HCC ≤2 cm are of two types. One with mean size of 12 mm is called as indistinct type without local invasiveness, the other with mean size 16 mm is called as distinct nodular type with local invasiveness. In the latter type, local metastases surrounding the nodule were observed in 10% of the cases and microscopic portal invasion upto 25%. This metastatic potential is called as Early HCC stage (Ye QH et al., 2003).

**Intermediate – advanced HCC**

Based on the performance status test values, the identification of invasive pattern of tumor was observed by the presence of vascular invasion or extrahepatic spread. It was divided into 2 sub groups

**Truly intermediate stage**

- Asymptomatic patients are those without any adverse prognostic factor or tumoral invasive pattern. They were observed to have 1, 2 & 3 years survival rate.
Advanced stage

- Patients with at least one adverse prognostic factor. They showed 1, 2 and 3 years of survival rate of patients with adverse factors of 29%, 16% and 8% respectively (Llovet et al., 1999).

End stage of HCC: It is the stage of HCC patients who are critical.

Symptoms of primary liver cancer

As cancer grows, the first few symptoms to develop may be quiet vague and nonspecific. For example: feeling generally unwell, feeling sick, nausea, loss of appetite, weight loss and tiredness.

Specific symptoms are

Abdominal pain, Jaundice- it is due to the bilirubin which is produced in the liver. When bile duct gets blocked, the bile and bilirubin cannot drain out from the liver so it leaks into the bloodstream. Swelling of the abdomen- due to cancer growth, the ascites which is fluid that builds up in the abdomen, occurs with various liver disorders.

Diagnosis

Diagnosis can be done by following techniques.

CT scan (CAT scan)

A procedure that delivers a series of detailed pictures of different parts of the body such as the chest, abdomen and pelvis. The picture could be computer linked to an X-ray machine.
This procedure is also called as computed tomography, computerized tomography or computerized axial tomography.

**MRI- Magnetic Resonance Imaging**

A procedure that uses a magnetic and radio waves. This procedure is also called as nuclear magnetic resonance imaging (NMRI).

**PET scan: (Position Emission Tomography Scan)**

A procedure to find malignant tumor cells in the body. A small amount of radioactive glucose (sugar) is injected into a vein. The PET scanner rotates around the body and makes a picture of where glucose is being used in the body. Malignant tumor cells shows up brighter in the picture because they are more active and take up more glucose than normal cells do.

**Stages of Liver Cancer**

**Stage I:** There is a single tumor and the cancer has not spread to the blood vessels, lymph nodes or any other part of the body.

**Stage II:** At this stage the cancer would not have spread to the lymph nodes or any other part of the body.

- It can be a single tumor that has grown into blood vessels of the liver.
- Several tumors that are less than 5cm but have not grown into the blood vessels.

**Stage III:** It is divided into 3 further groups

**Stage 3A:** There is more than one tumor and at least 1 of them, larger than 5cm. At this stage the cancer may not have spread to the lymph nodes or any other parts of the body.
Stage 3B: The cancer has grown into one of the main blood vessels of the liver (portal vein or hepatic vein), but cancer cells have not spread into lymph nodes or to any other part of the body.

Stage 3C: The cancer has spread into organs close to liver [not including the gall bladder], or through the lining that wraps around the internal organs of the abdomen. It has not spread to lymph nodes or any other part of the body.

Stage IV: This stage is divided into 2 further stages

Stage 4A: The cancer may be of any size and there may be more than one tumor. It may have grown into blood vessels or the organs around the liver. It has spread to lymph nodes but not to other parts of the body.

Stage 4B: The cancer may be of any size and there may be more than one tumor. It has grown into blood vessels or the organs around the liver. It may or may not have spread into lymph nodes, but has spread to another part of the body such as the lungs or bone (Cancer Research UK, 2013).

Different types of treatments used for Liver cancer

Surgery: A partial hepatectomy (surgery to remove the part of the liver where cancer is found) may be done. An entire lobe, or a larger portion of the liver along with some of the healthy tissue around it is removed, or a wedge of tissue can be removed. So rest of the liver tissues could take over the functions of liver and may regrow.

Liver Transplant: In a liver transplant, the entire liver is removed and replaced with a healthy donated liver.
Ablation Therapy: Ablation therapy removes or destroys tissues. Different types of ablation therapies are

Radiofrequency ablation: The uses of special needles that are inserted directly through the skin or through an incision in the abdomen to reach the tumor and high energy radio waves were produced to heat the needles and the tumor cells were killed.

Microwave Therapy: In this type of the treatment the tumor is exposed to high temperatures created by microwaves. This could damage and kill cancer cells or make them more sensitive to the effects of radiation and certain anticancer drugs.

Percutaneous Ethanol Injection: In this treatment a small needle is used to inject pure ethanol directly into a tumor to kill cancer cells. It is usually done by giving local anesthesia or general anesthesia.

Cryoablation: In this type of treatment an instrument is used to freeze and destroy cancer cells. It is also called as cryotherapy and cryosurgery. The surgeons use ultrasounds to guide the instrument.

Electroporation Therapy: The use of electrical pulse through electrodes placed in the tumor to kill cancer cells is known as electroporation therapy.

Embolization Therapy: It is a technique which is performed using certain substance to block or decrease the blood flow through the hepatic artery of the tumor, so that the cancer cells may not receive the essential oxygen and nutrients for its growth and hence they may die. Embolization therapy is used for the patients who cannot undergo surgery to remove tumor.
**Targeted therapy**: It is the treatment that uses drugs or other substances to identify and attack specific cancer cells without disturbing the normal non-cancerous cells. Adult liver cancer may be treated with targeted therapy.

**Radiation Therapy**: Radiation therapy is a treatment that uses high energy X-rays or other types of radiation to kill cancer cells.

**3D-Conformal Radiation Therapy**: In this type of therapy, the 3Dimensional picture of the tumor could be viewed, so that the highest possible dose of radiation to the tumor could be given preventing the damage or the destruction to the normal tissues as much as possible.

**The process of Carcinogenesis in HCC**

Buendia., 2000 and Thorgeirsson *et al.*, 2002, described the external stimuli that induce genetic alterations in mature hepatocytes leading to cell death and cellular proliferation. The upregulation of mitogenic pathways leads to the production of monoclonal population during the progression of chronic inflammation to fibrosis and cirrhosis. This monoclonal population forms dysplastic hepatocytes as a result of altered gene expression, telomerase erosions and even chromosomal aberrations. This process may occur ten to thirty years (Thorgeirsson *et al.*, 2002). This altered population results in forming foci of small cell dysplasia or more frequently, surrounded by fibrotic ring resulting in low grade dysplasia nodules (LDN) and high grade dysplastic nodules (HGDN). HGDN are considered as true pre neoplastic lesions and develop into malignant tumors in thirty percent of cases within 1–5 years (Seki *et al.*, 2000, Borzio *et al.*, 2003).
Apoptosis and cancer

The term apoptosis means cell death. It was introduced by Kerr and Colleagues in 1972. It is a greek term “apop – teo- sis” which means “falling off” (as in leaves from a tree or petals from a flower). It was used as a synonym of programmed cell death. Apoptosis was described based on its morphological characteristics, including cell shrinkage, membrane blebbing, chromatin condensation and nuclear fragmentation (Kerr et al., 1972 and Wyllie et al., 1980).

Apoptosis is a physiological process that eliminates the unwanted cells, an evolutionary process occurring in all multicellular organisms. Programmed Cell Death (PCD) is an important tool that provides space for new cells during the process of cell renewal. Apoptosis is highly regulated process that maintains the homeostatic cellular balance in a normal animal.

Stages of apoptosis

Apoptosis can be divided into 3 stages

Initiation: This phase mainly depends upon cell type and apoptotic stimulus

Integration/Decision: In this phase the activation of proteases, nucleases and other effector molecules occurs.

Execution/Degradation: This phase involves morphological and biochemical changes that are common to all apoptotic mechanism, regardless of the stimulus or initiation.

Apoptosis signaling pathway

Apoptosis is triggerred by multisignal pathway and regulated by complicated extrinsic and intrinsic ligands Figure 4.
Figure 4  Intrinsic and Extrinsic Apoptosis pathway
The process of apoptosis is controlled by various cell signaling pathways and it is involved in the regulation of cell fate (ie) death or survival. Caspases play the major role in the signal transduction process. These are highly conserved, cysteine dependent, aspartate – specific proteases. Caspases are of two types- they are initiator caspases like caspase 2, caspase 8, caspase 9, caspase 10, caspase 11, caspase 12. The other type of caspases are effector caspases namely caspase 3, caspase 6, and caspase 7. The activation of initiator caspases needs the help of specific oligomeric activator protein. But the effector caspases are activated only after the activation of the initiator caspases through proteolytic cleavage and then it involves in cell death program. The two major apoptosis pathways are distinguished based on the involvement of caspases or not.

**Caspase dependent pathway**

Caspase dependent apoptosis is the classic programmed cell death pathway. The caspase 8, caspase 9, caspase 12, caspase 7, caspase 3, cascade usually participate in apoptosis pathway.

A number of receptors like TNF alpha receptor, FasL receptor, death receptor and ion channels like calcium channel play the major role in apoptosis.

The TNF alpha induced caspase 8 dependent pathway relies on the TNF alpha receptor and activates caspase 8 through the death complex. Then the Bcl2 protein is activated, this Bcl2 family protein activation induces the mitochondria membrane to change and stimulates the cytochrome C release (Figure 5), the release of cytochrome C is a proapoptosis signal molecule activates caspase cascade and induce the apoptosis in the end.
Figure 5  Caspase dependent and Caspase Independent Apoptosis

Source: Tihomir Paul Obrenovitch, 2008
Caspase Independent Pathway

Caspases are inactive proenzymes activated by proteolytic cleavage. The disassembly of caspase 8 initiates the response to extracellular apoptosis ligands. This activates the complex associated with cytoplasmic death domain of many cell surface receptors for the ligands (Ashkenazi., 1998).

The activation of caspase 9, results in the release of cytochrome C from mitochondria (Liu X et al., 1996, Green and Reed., 1998) and this is stimulated when complexed with apoptotic protease activating factor I (AFP 1) and extra mitochondrial cytochrome C (Li P., et al., 1997). Caspase 3 seems to amplify caspase 8 and caspase 9 initiation signals. Caspase 8 and caspase 9 activates caspase 3 by proteolytic cleavage and caspase 3 then cleaves vital cellular proteins or other caspases (Thornberry and Lazebnik., 1998, Cyrs and Yuvan 1998).

An example for caspase independent apoptosis - Denis Martinvalet identified that granzyme A, could directly induce the ROS increase and caspase independent mitochondrial damage. The granzyme A, which is an endoplasmic recticular complex, gets translocated to nucleus and contribute to apoptosis. Apoptosis inducing factor [AIF] which is an important caspase independent pro- apoptosis factor would be released from mitochondria and translocate the nuclear DNA cleavage resulting in apoptosis. Recent researchers have identified the AIF production induces cell death, with the help of certain compounds like simvastatin, staurosporine, cadmium and so on (Wyllie et al., 1980).
Apoptosis and new therapeutic Strategies

As apoptosis could be manipulated to produce drastic change in cell death, the genes and the proteins controlling apoptosis are potential drug targets. Many cytotoxic drugs were already used to target apoptosis indirectly (Scott W Lowe and Athena W. Lin., 2000).

Following two strategies can be used as therapy

Targeting anti apoptotic activities

Over expression of anti-apoptotic Bcl2 family genes can promote tumorigenesis and chemoresistance. The functional inhibition of these proteins might be lethal to cancer cells

Restoring pro-apoptotic activities

In many cases when apoptosis is lost by a recessive mutation, by restoring the dysfunctional gene or activity it can promote massive cell death (eg). The re introduction of p53 into p53 mutant tumor cells can induce apoptosis by inactivating Rb and cdk2, which could be pro-apoptotic and produce a synthetic lethal effect in cells with a mutant Rb pathway (Chen et al., 1999).

Apoptosis and cancer therapy:

To identify agents that selectively kill tumor cells, many anticancer agents were developed using empirical screens, but the treatment sensitivity in carcinomas is less clear. Many researchers have proved to show marked correlations between p53 mutations and poor treatment response, whereas others see no effect (Schmitt and Lowe et al., 1999, Brown and Wouters, 1999).
Studies done using Bcl2 with drug resistance in patients proved to be a good prognostic indicator for breast cancer with high levels of Bcl2 (Brown and Wouters., 1999). Anticancer agents induce apoptosis in normal tissues as well as in tumors. Many pathologists identified apoptosis in tumors, realized that apoptotic cell death also occurs in the subset of normal tissues, by the effect of the “toxicity” associated with chemotherapy (Searle et al., 1975).

The moderate doses of radiation and chemotherapy induce apoptosis in the thymus, spleen etc, the same tissues that are subjected for the deleterious side effects of chemotherapy, where as these tissues in “p53” knockout mice showed much reduced apoptosis and cell loss following radiation or chemotherapy (Lowe et al., 1993, Clarke et al., 1993, Lotem and Sachs., 1993, Clarke et al., 1994, Merritt et al., 1994, Pritchard et al., 1998). Thus the drug induced apoptosis causes loss of normal cells and contributes to the side effects of cancer therapy.

**Importance of Phytochemicals**

There are epidemiological evidences representing the relationship between diets rich in fresh fruits and vegetables and decrease risks of cancer (Block et al., 1992, Steinmetz and Potter., 1996, Trock et al., 1990). It is generally assumed that the antioxidants such as vitamins, carotenoids, polyphenols and sterols present in the active dietary constituents are found to contribute protective effects (Shi et al., 2011). Plant based drugs have been used worldwide in traditional medicines for treatment of various diseases. India is called as the Botanical garden of the world as it is the largest producer of medicinal herbs (Arvind et al., 2010).

Vegetables and fruits are the chief sources of natural chemopreventives (Reddy et al., 2003), they might be present in animal source too (Kakagi et al., 2001). Most of the
Chemopreventive’s are complex mixtures and a few were isolated in the pure form and their structures were characterized (Cos et al., 2003).

Chemopreventives are of various categories namely carotenoids – [beta carotene, alpha carotene, leutin, lycopene etc] volatile oils – [Limonene, eugenol] fatty acids [omega 3 fatty acids], phytoestrogens – [Isoflavonoids, daidzein, genistein, flavonoids, stilbenes, resveratrol and lignans etc], organosulphurs [allicin], selenium, curcumin, coumarins, saponins, aminoacids and related compounds like glycosides, alkaloids, vitamins, anthocyanins etc. The phyto estrogens namely genistein and resveratrol are reported to reduce the incidence of various cancers (Cos et al., 2003).

**Side effects of Chemopreventive drugs**

Though synthetic chemopreventive agents were widely used in cancer treatment, it results in the drawbacks with high toxicity namely suppression of bonemarrow, alopecia, nausea, impotence, vomiting, immunosuppression etc. All these therapies are costly and not within the reach of common man (Hostettmann et al., 2001).

Sporn and Newton in 1979 coined the term “chemoprevention”. It was one of the efforts taken to prevent the impact of cancer in human population by using chemical agents (synthetic or natural). By this effort the process of carcinogenesis was inhibited or reversed.

**Difficulties involved in the development of chemopreventive agents**

- Lack of adequate animal models for testing chemopreventive efficacy in certain major cancer sites. Eg. Lung
- Longer duration is needed to observe cancer end points
Clinical trials are very expensive and large population is required for the study.

Difficulty of early screening of cancer, etc.

**Characteristics of an ideal chemopreventive agent**

According to Ito *et al.*, 1997, an ideal chemopreventive must fulfil the following characteristics.

- It should have the ability to inhibit initiation, promotion and progression.
- Nitrosamine formation should be blocked.
- It should be free from genotoxicity, carcinogenicity and general toxicity.
- It should not be a precursor for carcinogen or carcinogenesis.
- It must be easily and commercially available.

None of the chemopreventives fulfils all the above said characteristics.

Thousands of different species of plant have been reported historically, as useful agents for the treatment of cancer. In the 1950s, modern medicine began more systematically examining natural organisms as a source of useful anti-cancer substances (Mike *et al.*, 2010). Syam, Suvitha in (2011) stated the recent argument that "the use of natural products has been the single most successful strategy in the discovery of novel medicines". Akerele in 1988 stated that Medicinal plants continue to play a central role in the healthcare system of large proportions of the world’s population, and he added that over the past decade, herbal medicine has become a topic of global importance, making an impact on both world health and international trade.

Recently, a greater emphasis has been given towards the researches on complementary and alternative medicine that deals with cancer management. Plants have long history of use in the treatment of cancer (Balachandran *et al.*, 2005, Mukherjee *et al.*, 2001, Madhuri *et al.*, 2009).
Several studies have been conducted on herbs under a multitude of ethnobotanical grounds (Hartwell., 1969a, 1969, 1971, Pandey., 2002). Hartwell has collected data on about 3000 plants, those of which possess anticancer properties and subsequently been used as potent anticancer drugs.

Umadevi et al., 2013a stated that various types of anti-cancer plant are Zedoary (Curcuma zedoaria), Rodent Tuber (Typhonium flagelliforme), God’s Crown (Phaleria macrocarpa), Madagaskar Periwinkle (Catharanthus rosen), Artocarpus Integer (Selaginella corymbosa), Bamboo Grass (Loathatreum Gràcies), handsome (Taraxacum mongolicum), fruit makasar (Brucca javanica), Garlic (Allium sativum), Echo China (Smilax china), Sunflower (Helianthus annus), Leunca (Solanum nigrum), Job’s Tears (Coix Lachryma-Jobi), Bamboo Rope (Asparagus cochinchinensis) and others.

**Taxonomic Hierarchy**

- **Kingdom**
  - Plantae

- **Subkingdom**
  - Viridaeplantae

- **Infra kingdom**
  - Streptophyta

- **Division**
  - Tracheophyta

- **Sub division**
  - Spermatophytina

- **Infra division**
  - Angiospermae

- **Class**
  - Magnoliopsida

- **Super Order**
  - Asteranae
Order    - Solanales
Family   - Convolvulaceae
Genus    - Ipomoea
Species  - *Ipomoea batatas* (L). Lam.

*(Convolvulacea of North America., 2011) (Figure 6)*

**Description**

*Ipomoea batatas* is tuberous rooted perennial, top herbaceous, stems form a running vine up to 4 m long, usually prostrate and slender with milky juice *(Figure 7).* Stem – branches arises from short stem and usually not branched. Leaves ovate-cordate, borne on long petioles, palmately veined, angular or lobed. Flowers are greenish or purplish, axillary, funnel–shaped, seeds 1–4 per pod, flattened, hard coated *(Reed, 1976).*

**Ecology**

Sweet potatoes are reported to tolerate the annual precipitation of 3.1 to 42.9 dm, annual temperature of 8.4 to 28.5\(^\circ\) C, and pH of 4.3 to 8.7. It grows worldwide, with vast range of climatic condition. It grows in tropical and sub tropical climates. Sweet potatoes are fairly drought–tolerant. Soils like moderately deep, very friable fine sandy loams, sandy loams or loamy fine sands are very suitable for its cultivation. Excellent soils must have surface layers more than 30 cm in depth.
Figure 6 Structure of *Ipomoea batatas*
Figure 7  Structure of *Ipomoea batatas* Plant
**Origin of *Ipomoea batatas***

*Ipomoea batatas* is a tuberous perennial dicot, of family Convolvulacea, originated from Central America. Now it is widely cultivated in many parts of the world such as South East Asian countries (such as India, Philippine Islands and the South Seas Island) and in China (Reed., 1976, Zhao et al., 2007). It is commonly called as sweet potato but locally known as “anamo” or “odun kun” in Yoruba, “Dankali” in Hausa, “Ekomako” or “jioyibo” in Igbo languages.

**Sweet potato varieties in India**

<table>
<thead>
<tr>
<th>Sankarm</th>
<th>Gouri</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goutam</td>
<td>Sourin</td>
</tr>
<tr>
<td>Varsha</td>
<td>Kalinga</td>
</tr>
<tr>
<td>Sree Nandini</td>
<td>Sree Vardhini</td>
</tr>
<tr>
<td>Sree Ratna</td>
<td>Sree Bhadra</td>
</tr>
<tr>
<td>Sree Arun</td>
<td>Sree Varun etc</td>
</tr>
</tbody>
</table>

Kalinga variety of sweet potato was selected as the source for this study (Figure 8).

Kalinga Open pollinated sweetpotato variety, suitable for rainfed and irrigated uplands, medium duration (105–110 days) and yield range is 25–28 t/ha. Purple red skinned tuber with creamy white flesh. Dual-purpose variety used for food and animal feed. Useful for starch extraction in Jharkhand, Chattishgarh and West Bengal.
Figure 8  Kalinga Variety of Sweet potato
The following table shows the nutrient content of Sweet Potato.

<table>
<thead>
<tr>
<th>STAPLE</th>
<th>Sweet potato (raw, unprepared)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Component present (per 100 g portion)</td>
<td>Amount</td>
</tr>
<tr>
<td>Water (g)</td>
<td>77</td>
</tr>
<tr>
<td>Energy (kJ)</td>
<td>360</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>1.6</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>0.05</td>
</tr>
<tr>
<td>Carbohydrates (g)</td>
<td>20</td>
</tr>
<tr>
<td>Fiber (g)</td>
<td>3</td>
</tr>
<tr>
<td>Sugar (g)</td>
<td>4.18</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>30</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>0.61</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>25</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>47</td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td>337</td>
</tr>
<tr>
<td>Sodium (mg)</td>
<td>55</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>0.3</td>
</tr>
<tr>
<td>Copper (mg)</td>
<td>0.15</td>
</tr>
<tr>
<td>Manganese (mg)</td>
<td>0.26</td>
</tr>
<tr>
<td>Selenium (μg)</td>
<td>0.6</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>2.4</td>
</tr>
<tr>
<td>Thiamin (mg)</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Folk medicine

Hartwell, 1967–1971 reported that the leaf decoction of sweet potatoes were used as folk remedies for mouth and throat tumors. It is used as astringent, demulcent, bactericide, aphrodisiac, fungicide, laxative and tonic. Duke and Wain., 1981 reported that sweet potatoes were the folk remedy for bug bites, asthma, burns, convalescence, diarrhea, dyslactea, fever, nausea, splenosis, stomach distress and tumor.

Other medicinal properties of *Ipomoea batatas*

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riboflavin (mg)</td>
<td>0.06</td>
</tr>
<tr>
<td>Niacin (mg)</td>
<td>0.56</td>
</tr>
<tr>
<td>Pantothenic acid (mg)</td>
<td>0.80</td>
</tr>
<tr>
<td>Vitamin B6 (mg)</td>
<td>0.21</td>
</tr>
<tr>
<td>Folate Total (μg)</td>
<td>11</td>
</tr>
<tr>
<td>Vitamin A (IU)</td>
<td>14187</td>
</tr>
<tr>
<td>Vitamin E, alpha-tocopherol (mg)</td>
<td>0.26</td>
</tr>
<tr>
<td>Vitamin K1 (μg)</td>
<td>1.8</td>
</tr>
<tr>
<td>Beta-carotene (μg)</td>
<td>8509</td>
</tr>
<tr>
<td>Lutein+zeaxanthin (μg)</td>
<td>0</td>
</tr>
<tr>
<td>Saturated fatty acids (g)</td>
<td>0.02</td>
</tr>
<tr>
<td>Monounsaturated fatty acids (g)</td>
<td>0.00</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids (g)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Various biologically active compounds were found to be present in different parts of the plant and it was used to treat human diseases (Islam et al., 2003). *Ipomoea batatas* leaf was found to be the best source of Luetin, which was used in the prevention and treatment of age-related macular degeneration (Khachatryani et al., 2003).

Among the Himalayan tribes and Malaysians the plant juice and leafy tops are used for the control of hyperglycemia in diabetic patients (Chhetri et al., 2005). *Ipomoea batatas* leaf’s byproduct was documented to protect eyesight, prevent artherosclerosis, mutagenesis and carcinogenesis and accelerate metabolism (Han, 2000). Tubers (Ludvick et al., 2004) and leaves (Zhao et al., 2007) of *Ipomoea batatas* were found to effectively control hyperglycemia in diabetic patients.

White-skinned sweet potatoes were found to improve the abnormalities of glucose and lipid metabolism by reducing insulin resistance in obese Zucker fatty rats (Kusamo and Abe., 2000). It possessed antidiabetic activity. Nematocidal activity was observed in the whole plant (Mackeen et al., 1997).

*Ipomoea obscura* (L) belongs to the family “Convolvulaceae” and was found to be effective against dysentery. The paste of leaves of *Ipomoea obscura* was applied on ulcers, hemorrhoids and swellings (Christophe, 2002). *Ipomoea obscura* seeds and fruits are used to improve vision, to relieve pain, to improve breathing difficulty and it was also used as cleansing agents. *Ipomoea obscura* affects the central nervous system (Shahina, 1994). It is also a potent antioxidant (Srinivasan et al., 2008). *Ipomoea obscura* leaf, stem and seed extracts inhibited the growth of staphylococcus aureus, Bacillus subtilis, Bacillus steaothermophilus, Rhodococci sp,
Proteus vulgaris, Pseudomonas sp and Salmonella sp and proved its antibacterial activity (Arvind et al., 2010).

*Ipomoea batatas* (L) is from the family of convolvulaceae which is the world’s sixth largest food crop. The tubers of *Ipomoea batatas* commonly known as sweet potato are consumed as a vegetable globally. It is also called Kamote, Lapni, yams and tugi in various parts of the world. The tuber is tapered and long, and the skin may be red, purple or brown and white in color. The flesh may be white, yellow, orange or purple (Miyazaki et al., 2005, Cambie and Ferguson., 2003). The peels of *Ipomoea batatas* tubers showed a potent wound healing activity, which may be due to an underlying antioxidant mechanism (Vandana Panda et al., 2011).

The plants belonging to the genus *Ipomoea* (convolvulacea) consists of a number of species distributed in tropical and sub tropical countries. Some of these plants were frequently used in folk medicine for treatment of several diseases. *Ipomoea* pes-caprae known as salsa - da – praia was used in folk medicine against inflammation and gastrointestinal disorder and as an analgesic agent (Souza et al., 2000). Pongprayoon et al., 1991 stated *Ipomoea* pes-caprae as a medicinal plant used in the treatment of headache and various types of inflammation including jellyfish sting dermatitis.

The plant *Ipomoea Carnea* belongs to family Convolvulaceae, was used in ancient system of medicine in many countries. The plant *Ipomoea Carnea possess* immense potential as an Anti-Inflammatory Activity, Antioxidant Activity, Antidiabetic Activity, Antimicrobial Activity, Wound Healing Activity, Immunomodulatory Activity, Cardiovascular Activity, Embryotoxic effect, Antifungal Activity, Hepatoprotective Activity, Inhibition Activity and Anxiolytic Properties. Nandkumar P1., 2011, identified the similarity between Ipomoea carnea and wood. He stated that the soda lignin and soda anthraquinone lignin obtained from wood and
Ipomoea carnea were almost same, containing vanillin and syringaldehyde. Ipomoea carnea had been found to be used for making papers (Nandakumar.P2, 2011).

Ipomoea aquatica is used for treatment of diabetes (indigenous medicine in Sri Lanka) (Jayaweera, 1982; Malalavidhane et al., 2001). Venom antidote as emetic, diuretic, purgative, to treating debility, liver complaints, ringworm, leucoderma, leprosy, fever (Ghani, 1989; Mamun, et al., 2003), and for nosebleed and high blood pressure (Prasad et al., 2005a).

Ipomoea batatas was used in the treatment of tumors of the mouth and throat. Leaves decoctions of Ipomoea batatas are used as alterative, aphrodisiac, astringent, bactericide, demulcent, fungicide, laxative and tonic. Sweetpotato is used for treating asthma, bugbites, burns, catarrh, convalescence, diarrhea, dyslactea, fever, nausea, renosis, splenosis, stomach distress, tumors, and whitlows (Duke & Wain, 1981). In region of Kagawa, Japan, a variety of white sweet potato has been eaten raw for treating anemia, hypertension and diabetes (Ludvik et al., 2004). Ipomoea is used in the treatment of rheumatism and inflammations (Ferreira et al., 2006). I. campanulata was an antidote to snake poison (Singh et al., 2003). In Thailand I. carnea was used against Immunodeficiency Syndrome (AIDS) (Thailand) (Woradulayapinij et al., 2005) and to treat hypertension (Gabon) (Lamidi et al., 2000). The powdered root of I. digitata was used in emaciation of children and also as tonic, alterative, aphrodisiac, demulcent, lactogogue, and cholagogue. Decoctions of root were used against constipation (Singh et al., 2004).

Ipomoea batatas, Agaricus blazei and Smallanthus sonchifolius are known to favorably influence diabetes mellitus. In order to clarify their antidiabetic efficacy and hypoglycemic mechanisms, Atsuko Niwa et al., (2011), treated streptozotocin-induced diabetic rats, with powdered Ipomoea batatas (5 g kg\(^{-1}\) d\(^{-1}\)), Agaricus blazei (1 g kg\(^{-1}\) d\(^{-1}\)) or Smallanthus
sonchifolius (4 g kg\(^{-1}\) d\(^{-1}\)) daily in oral feed for 2 months. They identified that the treatments with *Ipomoea batatas* and *Agaricus blazei* significantly suppressed the fasting plasma glucose and hemoglobin A1C levels, and restored body weight loss during diabetes.

Sathish Rengarajan *et al.*, 2012, worked on peptic ulcer which is one of the most important gastrointestinal disorders using Ethanolic extract of the dietary tuber *Ipomoea batatas* in male Wistar albino rats. The antiulcer activity was evaluated by the Pylorus Ligation (PL) and cold restraint stress (CRS) Induced Ulcer models. In PL model EEIB significantly (*p* < 0.01) reduced the ulcer index by 55.24% and 61.45% at 250 & 500 mg/kg doses respectively. In CRS model, both the doses of EEIB significantly (*p* < 0.01) reduced ulcer index by 51.35% (250 mg/kg) and 75.68% (500 mg/kg). The *Ipomoea batatas* roots possess antiulcer activity as evidenced by its significant inhibitory effects on PL and CRS induced ulcers.

Olubobokun *et al.*, 2014 described the effect of dried aqueous extract of *Ipomoea batatas* on food intake in male Wistar rats. He observed that in the extract-treated groups, the food intake was significantly reduced at *P* < 0.01 in a dose dependent manner when compared with the control group. Based on the results Olubobokun *et al* concluded that the consumption of IB caused a reduction in food intake probably by reducing appetite and increasing satiety.

The experiments done by Daniele Hermes *et al*, 2013 proved *Ipomoea batatas* to posses wound healing property in wistar albino rat model. They stated that the Ointment based on white sweet potato at 2.5% effectively triggered the healing of cutaneous wound created by the excision on the back of Wistar rats, increased number of cells undergoing metaphase and tissue re-epithelialization regardless the time of wound treatment. They added that the tuber flour potentially prevented ethanol-induced gastric ulceration by suppressing edema formation and partly protecting gastric mucosa wrinkles.
Aan Royhan et al., 2009, subjected White-skinned sweet potato’s flour suspension (100, 200, 400 and 800 mg/kg BW/day) orally to Streptozotocin induced diabetic rats. White-skinned sweet potato had a significant blood glucose lowering effect and increased the number of pancreatic beta cells and insulin expression in a dose dependent manner in diabetic condition. From the results they suggested that white-skinned sweet potato produced hypoglycemic activity by inducing pancreatic beta cells regeneration and increasing insulin expression.

When sweet potato proteoglycans were given to hyperlipidemic rats, it showed hypolipidemic effect based on the dosage. Jianquan Kan et al., (2014), stated that the proteoglycans isolated from Ipomoea batatas showed significantly (P < 0.05) reduced serum total cholesterol (TC), triacyl glycerol (TAG), low density lipoprotein cholesterol (LDL-C), apolipoprotein (Apo B) levels and induced serum high density lipoprotein cholesterol (HDL-C), Apo- AI, Lecithin cholesterol acyl transferase (LCAT).

Li F et al., (2009) identified that the flavonoids isolated from Ipomoea batatas leaves (FIBL) posses antidiabetic effect on alloxan induced diabetic mice. They observed that FIBL treatment resulted in a significant decrease in the concentration of fasting blood glucose (FBG), total cholesterol (TC) and triglyceride (TG) in diabetes mellitus mice.

Furthermore, FIBL significantly increased body weight (bw) and serum high-density lipoprotein cholesterol (HDL-c) level. They concluded that FIBL at the dose of 100 mg/kg body weight exhibited the optimal effect and FIBL can control blood glucose and modulate the metabolism of blood lipid in diabetes mellitus mice.

Yoshikawa K et al., (2010) isolated four resins namely ipomotaosides A-D (1–4) from the dried aerial parts of Ipomoea batatas, and experiments were performed to prove their anti-
inflammatory activity against cyclooxygenase (COX-1 and 2). The structures of 1–4 were elucidated by analysis of spectroscopic data and by chemical derivatization.

**Taxonomic Hierarchy**

Kingdom - Plantae

Subkingdom - Viridaeplantae

Infra kingdom - Streptophytla

Division - Tracheophyta

Subdivision - Spermatophytina

Infradivision - Angiospermae

Class - Magnoliopsida

Super Order - Asteranae

Order - Solanales

Family - Solanaceae

Genus - Solanum

Species - Solanum tuberosum

(Planetary Diversity 2011) (Figure 9)
Figure 9 Structure of *Solanum tuberosum*

*Solanum tuberosum* plant
Description

*Solanum tuberosum* plant is erect or clambering succulent herb more than 1 meter. The stems are winged, with tuberiferous stilens just below the soil surface (Figure 10). Leaves alternate, impairpinnate, short-stalked, 10–30 cm long, 5–15 cm wide. The leaflets opposite or alternate, very unequal in size and shape, the larger often petioluate. Flowers white or blue, pedunculate in lateral, many flowered cymes, the hairy peduncle 5–15 cm long. Calyx campanulate, 5–lobate, 1.5–2 cm in diameter, the lobes acute or acuminate. Corolla twice as long as calyx, 3.5–4 cm in diameter. Anthers free, erect, yellow. Fruit aglobose 2–celled berry, yellowish green. (Ochse, 1931; Vilmorin – Andrieux, 1885).

Ecology

Ranging from Borel Moist to wet through Tropical very dry to wet forest life zones, potato was reported to tolerate annual precipitation of 0.9 to 41.0 dm, annual temperature of 3.6 to 27.8°C, and pH of 4.2 to 8.2. Potatoes grow well on a wide variety of soils, sandy loams, loams and peats. Soil moisture tension between 40 and 60 centibars seem to produce the best yield (Duke, 1978; Smith, 1981).

Historical introduction and taxonomy of potato

Molecular taxonomic evidence stated that farmers of the Andes of Southern Peru and Northern Bolivia have given rise to a single domestication from the northern group of members of the *Solanum brevicaule* complex of species more than 7,000 years ago (Kang and Priyadarshan., 2007).
Figure 10 Structure of *Solanum tuberosum* Plant

- flower
- inflorescence
- fruit
- leaflets
- compound leaf
- main stems
- lateral stem
- mother tuber
- stolons
- tubers
- roots

INTERNATIONAL POTATO CENTER (CIP)
The domestication of *Solanum stenotomum* has led to the cultivation of six most widely used species in South America which include *Solanum tuberosum*. It has been classified into genetically distinct subspecies Andigena and Chilean tuberosum (Kang and Priyadarshan., 2007).

In 1537, the conquistadors invaded Peru and in the year 1570, the European continent received its first introduction of potato, and they believed it has been obtained from both the Andes and Chile (Kang and Priyadarshan., 2007). Within five centuries, this diverse and highly adaptable tuber *Solanum tuberosum* has spread from its original heartland South America from high Andes to all elevated zones in temperate regions of all the continents. Then its production was found to increase most rapidly in the warm, humid, tropical Asian lowlands during the dry season (Vander Zaag., 1984).

**Potato varieties in India**

<table>
<thead>
<tr>
<th>Kufri Swarna</th>
<th>Kufri Sutlej</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kufri Surya</td>
<td>Kufri Sindhuri</td>
</tr>
<tr>
<td>Kufri Sherpa</td>
<td>Kufri Shailja</td>
</tr>
<tr>
<td>Kufri Safed</td>
<td>Kufri Pukhraj</td>
</tr>
<tr>
<td>Kufri Neela</td>
<td>Kufri Naveen</td>
</tr>
<tr>
<td>Kufri Muthu</td>
<td>Kufri Megha</td>
</tr>
<tr>
<td>Kufri Jyoti</td>
<td>KCM (2708)</td>
</tr>
<tr>
<td>Kufri Badshah</td>
<td>Kufri Lauvkar, etc.</td>
</tr>
</tbody>
</table>
Kufri Muthu variety of Potatoes was selected as the second source for this study.

Easy to cook, texture floury, flavour mild, free from aftercooking discoloration (Figure 11). Moderately resistant to late blight, immune to wart. Tolerant to hopper burn. Suitable for cultivation in South Indian hills.

The following table shows the nutrient content of Potato

<table>
<thead>
<tr>
<th>Component present in (per 100g portion)</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (g)</td>
<td>79</td>
</tr>
<tr>
<td>Energy (kJ)</td>
<td>322</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>2.0</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>0.09</td>
</tr>
<tr>
<td>Carbohydrates (g)</td>
<td>17</td>
</tr>
<tr>
<td>Fiber (g)</td>
<td>2.2</td>
</tr>
<tr>
<td>Sugar (g)</td>
<td>0.78</td>
</tr>
<tr>
<td>Calcium (mg)</td>
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</tr>
<tr>
<td>Iron (mg)</td>
<td>0.78</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>23</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>57</td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td>421</td>
</tr>
<tr>
<td>Sodium (mg)</td>
<td>6</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>0.29</td>
</tr>
</tbody>
</table>
Figure 11 Kufri Muthu variety of *Solanum tuberosum*
<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper (mg)</td>
<td>0.11</td>
</tr>
<tr>
<td>Manganese (mg)</td>
<td>0.15</td>
</tr>
<tr>
<td>Selenium (μg)</td>
<td>0.3</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>19.7</td>
</tr>
<tr>
<td>Thiamin (mg)</td>
<td>0.08</td>
</tr>
<tr>
<td>Riboflavin (mg)</td>
<td>0.03</td>
</tr>
<tr>
<td>Niacin (mg)</td>
<td>1.05</td>
</tr>
<tr>
<td>Pantothenic acid (mg)</td>
<td>0.30</td>
</tr>
<tr>
<td>Vitamin B6 (mg)</td>
<td>0.30</td>
</tr>
<tr>
<td>Folate Total (μg)</td>
<td>16</td>
</tr>
<tr>
<td>Vitamin A (IU)</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin E, alpha-tocopherol (mg)</td>
<td>0.01</td>
</tr>
<tr>
<td>Vitamin K1 (μg)</td>
<td>1.9</td>
</tr>
<tr>
<td>Beta-carotene (μg)</td>
<td>1</td>
</tr>
<tr>
<td>Lutein+zeaxanthin (μg)</td>
<td>8</td>
</tr>
<tr>
<td>Saturated fatty acids (g)</td>
<td>0.03</td>
</tr>
<tr>
<td>Monounsaturated fatty acids (g)</td>
<td>0.00</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids (g)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Potato consumption products**

Potatoes can be purchased fresh, baked, roasted, boiled or steamed for home made consumption (Verughenhil and Bradshaw, 2007). Processed potatoes could also be purchased, which accounts for 60% of developing nation’s mode of consumption. The potato chips
originated in Newyork in 1853 in a hotel kitchen in Saratoga Springs (Verughenhil and Bradshaw., 2007).

Potatoes were also used to develop other products comprising the global market in developing nations. Frozen potato products other than the French fries include waffles, wedges, hased brown potatoes, rosti, performed mashed potatoes, patties, potato rounds, diced potatoes, bay roasts and a variety of shaped potato products with child appeal (Verughenhil and Bradshaw., 2007).

In restaurants and catering business, potatoes were popularly used as processed ones in canned goods. It was also used as live stocks. Potatoes can be used primarily as a starch source, and it could be processed for the production of alcohol (Sleeper and Poehlman., 2006).

Folk medicine

In Folk medicine potato was used as the remedy for burns, cough, cyctitis, fistula, scurvy, spasms, prostatitis, tumors and warts (Duke and Wain 1981, Hartwell., 1967–1971). To alleviate corns, boiled tuber was used. The tea made from potato peels was said to be used as folk remedy for tumors. To protect from frost bite the mealy flour of baked potato was oiled and applied (Grieve, 1931). Raw potatoes were tied behind the ears, by Europeans for delirium (Duke, 1984b).

Potato and cancer

Solanaceae family posses about 2000 species, which includes plants such as tobacco, tomato, egg plant, pepper and potato. Potato was considered as a good source of antioxidants like ascorbic acid and alpha- tocopherol which act synergistically (Byers and Perry., 1992). Potatoes
are potent antioxidants by containing flavones aglycones, a major group of plant phenol (Ding et al., 2010). It is a good source of glutathione (Jones et al., 1992).

Studies have shown that potato extracts have potential antioxidant activities which are active against toxic chemicals in both In vitro (Al – Saikhan et al., 1995, Mohalaly et al., 2010) and In vivo (Singh et al., 2008).

Potato peel was found to contain phenolic acids (Lisinsika and Leszezynski., 1987). Fisher and Bipp in 2005 recognised glucaric acid to be present in potato peel sludge. Potato peel had the highest antioxidant activity and flavonoids (Sarhan et al., 2010). Protein concentrates prepared from potatoes were found to have excellent nutritional quality when measured in terms of protein efficiency ratio (PER = 2.90), Biological value (BV = 79.5), net protein utilization (NPU = 74.2) and Nitrogen retention (Nestares et al., 1993). Rodriguez de Sotillo et al., 1998 stated that potato peel extracts have proved to posses bacteriostatic and bacteriocidal activity and it was found to be a good source of natural antioxidant preservative in wide food applications.

Solanaceae family comprises of a number of plants widely known for the presence of variety of natural products of medicinal significance mainly steroidal lactones, glycosides, alkaloids and flavanoids. *Solanum nigrum* L. a member of the Solanaceae has a wide range of medicinal applications (Yogananth et al., 2009). Solasodine is an important phytochemical of Solanaceae plant including *S. lyratum* Thunberg. It was commonly used in the traditional Chinese medicines in China, Taiwan and Korea. It was used to regulate the immune function and as a treatment for allergic responses (Kang et al., 1997).

Solasodine was also found to show antifungal activity. It was investigated using *Saccharomyces cerevisiae* GL7 and *Prototheca wickerhamii* (P. wickerhamii). Solasodine
directly or indirectly interfered with the synthesis and function of DNA in S. cerevisiae and P. wickerhamii and proved its antifugal effect (Wang et al., 2000). Solasodine isolated from Solanum trilobatum was examined for anti-inflammatory activity in acute and chronic inflammatory animal models. Solasodine exerted statistically significant and dose-dependent anti-inflammatory activity in carrageenan-induced rat paw oedema. Topical application of solasodine significantly inhibited the ear inflammation induced by multiple applications of tetradecanoyl-phorbol 13-acetate (Pandurangan et al., 2011).

The steroidal glycoalkaloids are the family of secondary metabolites produced by Solanaceous plants, including potato, tomato and eggplant. This Steroidal glycoalkaloids have antimicrobial, insecticidal and fungicidal properties providing resistance against several insect pests and herbivores (Rodriguez-Saona et al., 1999). Further, it is also used to treat cancer of liver, lung, esophagus and blood, as well as tumours and warts (Yalin et al., 2005, Sun et al., 2006, Ren et al., 2006, Kuo et al., 2009).

*Solanum nigrum* Linn. (Solanaceae) which was commonly known as ‘Black nightshade’ was extensively used in traditional medicine in India and other parts of world to cure various diseases like liver disorders, chronic skin ailments (psoriasis and ringworm), inflammatory conditions, painful periods, fevers, diarrhoea, eye diseases, hydrophobia etc (Kritikar and Basu, 1935).

Potato juice was stated to be unmatched in the treatment of gastric acidity and gastric ulcer, by calming and healing the digestive tract. Umadevi and her colleagues in 2013 have reported that *Solanum tuberosum* acts as an antispasmodic, diuretic and emollient. The cooling effect of raw potato slices brings fast relief from swelling (and itching) caused by contact dermatitis and insect bites. Potato juice has proved to reduce acidosis and heal gastrointestinal
inflammation because it contains compounds that coat the lining of the stomach. Potato proteins such as proteinase inhibitors were proved to exhibit antimicrobial activity during infection. It was observed to produce defense against pathogens and invading organisms (Plate et al., 1993).

Phytochemical screening of *S. trilobatum* showed the presence of carbohydrates, saponins, phytosterols and tannins in leaf, whereas, stem possess carbohydrates, saponins, phytosterols, tannins, flavonoids and cardiac glycosides as major phytochemicals. *S. trilobatum* was reported to cure numerous diseases viz., tuberculosis, respiratory problems and bronchial asthma. *S. trilobatum* was reported to harbour hepatoprotective activity, antimicrobial activity, antioxidant activity, cytotoxic activity, haemolytic activity, immunomodulatory activity and anti-inflammatory properties (Juhi Sahu et al., 2013).

Phytochemical studies of *Solanum torvum* indicated that fruits of this species have good concentrations of various alkaloids, flavonoids, saponins, tannins, and glycosides in sufficient quantities to exert pharmacological effects. *Solanum torvum* was found to possess both sedative and diuretic effects. The leaves of *Solanum torvum* was used as a haemostatic. Therefore, fruit are not only used for nutritive purposes but also fruit decoctions are effective for cough ailments and are considered to be effective medicine in cases of liver and spleen enlargement. The ripened fruits are used in the preparation of tonic and haemopoietic agent and also for the treatment of pain (Kala, 2005).

Ndobia et al., 2007 identified the potential anti-inflammatory and analgesic properties of Aqueous extracts of *S. torvum*. *Solanum torvum* was one of the most pharmaceutically important members of the potato family. The species is included among the ingredients of various indigenous herbal medicines for treating a number of diseases. Moreover, anticancer phenolic
Compounds have also been isolated from fruit and leaves of *Solanum torvum* (Zubaida Yousaf et al., 2013).

Olubobokun *et al.* in 2013, worked on to determine the effect of *Solanum tuberosum* on food intake, fasting blood glucose level and subsequent effect on body weight with a view to recommend it as a diet for the obese population. They carried out their experiment using wistar albino rats. *Solanum tuberosum* significantly (*P* < 0.05) reduced food intake, fasting blood glucose level and body weight compared to control. The decrease was most significant in the group administered 300mg/kg body weight of the *Solanum tuberosum* extract. The effect of *Solanum tuberosum* extract was time dependent and significant (*P* < 0.05) decrease was observed in the third week compared to the first week. So they concluded that *Solanum tuberosum* can serve as a diet in the management of body weight.

Paola Bontempo *et al.*, 2013 aimed to characterize and measure the concentration of anthocyanins in pigmented potatoes and to evaluate their antioxidant, antimicrobial and anti-proliferative effects in solid and hematological cancer cell lines. The outcome of their work stated that the Gram-positive bacterium Staphylococcus aureus and the fungus Rhyzoctonia solani were the most affected microorganisms. The Potato extract showed a higher reducing capability, in different cancer cell models. They concluded that the anthocyanins cause inhibition of proliferation and apoptosis in a dose dependent manner.

Nazareth *et al.*, 2014 showed that the *Solanum tuberosum* extract had great potential in preventing the overproduction of free radicals and anti proliferative effect on HepG2 cell lines and its cell viability on normal cell lines revealed its anticarcinogenic property.

Potato peel a waste by product of potato processing is found to be a good source of both dietary fiber and polyphenols. Both dietary fibers and polyphenols have been reported to exert
antihypercholesterolemia. Afify et al., 2011, examined the attenuating influence of dietary potato peel powder on hypercholesterolemia and various oxidative stress-associated with biochemical parameters in hypercholesterolemic rats. They identified that the potato peel powder to reduce the weight on hypercholesterolemic state and reducing hypercholesterolemic complications. In addition, potato peel powder also served to improve the lipid profile (cholesterol, total lipid, triglycerides, LDL-C and HDL-C) and haematological parameters and to reduce the blood glucose level in hypercholesterolemic rats and could be used in obese people for body loss.

Saeid Abbasi-Maleki in 2015 investigated on the antibacterial effects of ethanolic extract on Streptococcus pyogenes, Staphylococcus aureus, Pseudomonas aeruginosa and Klebsiella pneumonia. He used Solanum tuberosum peel ethanolic extract for his study. He found that the SE peel extract has antibacterial activity and its effect on gram-positive bacteria was more pronounced than on gram-negative bacteria.