Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells, if the spread is not controlled, it can result in death. Cancer is caused by both external factors (tobacco, infectious organisms, chemicals and radiations) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism). These causal factors may act together or in sequence to initiate or promote cancer. Cancer represents a tremendous burden on patients, families, and societies. It is one of the leading causes of death in the world and is still increasing, particularly in developing countries. Cancers in all forms are causing about 12 per cent of deaths throughout the world. In the developed countries cancer is the second leading cause of death accounting for 21% (2.5 million) of all mortality. In the developing countries cancer ranks third as a cause of death and accounts for 9.5% (3.8 million) of all deaths (IARC, WHO, American Cancer Society). By 2030, it is estimated that 20-25 million new cases of cancer will be diagnosed each year with 13-16 million cancer deaths annually. Cancer has become one of the ten leading causes of death in India. It is estimated that there are nearly 1.5 to 2 million cancer cases at any given point of time. Over 7 lakh new cases of cancer and 3 lakh deaths occur annually due to cancer and 45% cancer among men and 14% among women are due to tobacco use.

Data from population-based registries under National Cancer Registry Programme indicate that the leading sites of cancer are oral cavity, lungs, oesophagus and stomach amongst men and cervix, breast and oral cavity amongst women. Two third of cancer in India are life style associated and this in principle can be prevented.

Breast cancer is the most common cancer among women worldwide and cervical cancer ranks as the 1st most frequent cancer among women in India, and the most frequent cancer among women between 15 and 44 years of age.

Tumours can be benign or malignant. Benign tumours are not cancerous. They can often be removed by surgery and in most cases do not spread to other parts of the body. Most benign tumours are not life threatening. Malignant tumours are cancerous, are generally more serious than benign tumours and may be life-threatening. In some cases, the original cancer, also called the primary tumour, can spread to other parts of the body via the bloodstream or lymphatic system to form new, or secondary, tumours.

According to the modern understanding of cancer, it is a disease that is primarily associated with genetic and epigenetic alterations by specific mutations in specific key regulatory genes. A number of genes that are specifically mutated in malignant cell have been defined to date. They can generally be divided into two groups: oncogenes and tumour suppressor genes. Oncogenes take part in malignant transformation due to activating mutations such as amplification, small mutations
or translocations. The function of tumour suppressor genes on the other hand seems to be to protect the normal cell from developing into a cancer cell, and a loss of their function leads to malignant transformation (Ishii et al., 2010).

In humans tumourigenesis is a multistep process that drives the progressive transformation of normal human cells into highly malignant derivatives. It has been suggested that the vast catalog of cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth: self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. Each of these physiologic changes acquired during tumour development represents the successful breaching of an anticancer defense.

Chronic inflammation is closely linked to the tumourigenic pathway as is evident from numerous lines of evidence. First, inflammatory markers such as cytokines (such as TNF, IL-1, IL-6, and chemokines), enzymes (such as COX-2, 5-LOX, and matrix metalloproteinase [MMP]), and adhesion molecules (such as intercellular adhesion molecule 1, endothelium leukocyte adhesion molecule 1, and vascular cell adhesion molecule 1) have been closely linked with tumourigenesis. Second, all of these inflammatory gene products have been shown to be regulated by the nuclear transcription factor, NF-κB. Third, NF-κB has been shown to control the expression of other gene products linked with tumourigenesis (Villegas et al., 2010). In several types of cancer, particularly gastric carcinoma and colon adenoma, COX-2 is up-regulated generating pro-tumourigenic prostaglandins that can promote cell growth, angiogenesis and suppression of immunity. iNOS produces large amounts of nitric oxide involved in the initiation, promotion and progression of tumours (McConnell and Yang, 2009).

The majority of deaths (about 90%) associated with cancer are due to the metastasis of the original tumour cells to sites distant from the initial or primary tumour. Cancers are capable of spreading throughout the body by two mechanisms: invasion and metastasis. Invasion refers to the direct migration and penetration by cancer cells into neighboring tissues. Metastasis refers to the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and then invade normal tissues elsewhere in the body. The capability for invasion and metastasis enables cancer cells to escape the primary tumour mass and colonize new terrain in the body where, at least initially, nutrients and space are not limiting. Invasion and metastases occur within a tumour-host microenvironment, where stroma and tumour cells exchange signals that modify the local extracellular matrix
(ECM), stimulate migration, and promote proliferation and survival (Brooks et al., 2010).

The degradation of the ECM and components of the basement membrane caused by proteinases, such as MMPs, cathepsins, and plasminogen activator (PA), play a critical role in tumour invasion and metastasis. Among these proteinases, MMPs, MMP-2 (gelatinase A, 72 kDa) and MMP-9 (gelatinase B, 92 kDa) are the most vital enzymes for the degradation of the main constituent of the basement membrane, type IV collagen and are therefore deeply involved in cancer invasion and metastasis. Therefore, the inhibition of migration or invasion mediated by MMPs or u-PA could be a preventive way of cancer metastasis (Friedl and Wolf, 2003).

The transcription of MMPs or u-PA gene is regulated by upstream sequences, including motifs corresponding to NF-κB, AP-1 or Ets-1 binding sites. Indeed, an activation of NF-κB and AP-1, are involved in many pathological processes, such as inflammation, cancer cell adhesion, invasion, metastasis and angiogenesis. Therefore, it has been suggested that suppression of the NF-κB, c-Jun and c-FOS activities may enable a potential in blocking tumour initiation, promotion and metastasis, as well as blocking the factors that bind to these regulatory elements, and therefore represents an appropriate approach to inhibit the synthesis of MMPs or u-PA.

In order for tumours to progress, they must acquire angiogenic ability, termed the angiogenic switch. Like normal tissues, tumours require an adequate supply of oxygen, nutrients, and an efficient way to remove waste products. Thus, gaining access to the host vascular system and the generation of a tumour blood supply are considered as a rate-limiting step in tumour progression (DeVita, 2008). The physical steps occurring during angiogenesis are well documented. Firstly pericytes retract from the abluminal surface of capillaries. Endothelial cells then release and activate proteases such as uPA and MMPs which degrade the extracellular matrix surrounding the existing capillaries. Endothelial migration and proliferation then occur, followed by the alignment of endothelial cells into tube-like structures, which ultimately anastomose to form new capillaries. Anti-angiogenic treatment may be aimed at any of these stages (Eatock et al., 2000). The angiogenic switch can occur at different stages of the tumour-progression pathway, depending on the tumour type and the microenvironment. Induction of the angiogenic switch from vascular quiescence depends on the balance between anti- and pro-angiogenic factors. These factors can be induced by multiple molecules that are released by both cancer cells and stromal cells. Pro-angiogenic factors such as members of the VEGF family have proven to be significant proto-oncogenes.
Apoptosis, or programmed cell death, is yet another process that is subverted by a tumour cell (Jacotot et al., 2000). In a normal cell, a series of 'checkpoints' must be met before the cell permits itself to divide. If irreparable damage to its DNA is present, the cell undergoes apoptosis, thus ensuring that its mutated DNA is not transmitted to the progeny cells. The molecules that regulate this process of apoptosis are often themselves mutated in cancer cells, which are then able to escape the checks and balances that a normal cell must undergo before it can divide.

Current cancer therapeutic modalities include surgery, radiotherapy, hormonotherapy, chemotherapy, and the targeting of specific compounds. These strategies can lead to complete remission, yet the vast majority of cases experience stable disease that eventually relapses and develops into distant metastases. (Locher et al., 2010) Many chemotherapeutic agents used to treat malignant diseases damage lymphocytes and consequently suppress cell-mediated immunity (Barrett, 2009). Hence there is a great need for effective alternate therapies. In the last 3 decades, the use of complementary and alternative medicine (CAM) has increased in popularity in both the worldwide general population and in patients with cancer. The goals of CAM are to increase the efficacy of conventional cancer treatment programs, reduce symptoms, and improve quality of life for patients with cancer (Levine, 2010). Plants and plant-derived products are considered excellent sources for the discovery and development of such novel cancer chemoprotective and chemotherapeutic agents. Several classes of natural compounds have been evaluated for this purpose. Each of these classes of plant-derived compounds or extract interacts with the host to confer a preventive benefit by regulating cellular signaling of proliferation and death (Patwardhan and Gautam, 2005).

Ipomoea obscura (Linn.) Ker-Gawl, is a very common, paleotrophic perennial herb belonging to the genus Convolvulaceae (Jenett-Siemens et al., 2003). Most of Ipomoea species has been reported to possess several pharmacological activities such as anti inflammatory. I. obscura is mentioned as an important medicinal plant in the ancient Ayurvedic literature. An indole alkaloid Ipobscurine has been reported in this plant (Savithramma et al., 2007).

Among several types of compounds obtained from plants, alkaloids have traditionally been of interest due to their pronounced and various physiological activities in animals and humans (Kutchan, 1995). Ipobscurine, An indole alkaloid present in I. obscura is structurally characterized as serotonin hydroxyeinnamic acid amide-type conjugates with a second phenyl propanoid moiety forming ether with the 5-OH position of the indole nucleus (Jenett-Siemens et al., 2003). The β-carboline alkaloids present in medicinal plants such as Peganum harmala and
Eurycoma longifolia have recently drawn attention due to their anti-tumour properties. Those plants have been used for the treatment of various diseases including cancers and malaria in oriental traditional medicine for 2 millennia (Lamchouri et al., 1999). The major active components in the extracts were identified to be harmine, harmaline, harmalol and Harman (all β-carbolines) (Funayama et al., 1996). Various authors have undertaken studies on the antibacterial, antifungal and antiviral effects of Peganum harmala seeds, but much study on the anti-tumour activity are not to be found in the literature. But there are a very few reports on Harmine giving a hope for their anti-tumour properties that have to be explored (Lamchouri et al., 1999; Yu et al., 2003).

As part of our search for natural product-based anti-angiogenic agents, we studied the effects of the I. obscura, Ipobscurine an alkaloid obtained from I. obscura and Harmine on the tumour progression using both in vivo and in vitro models. We also studied the mechanism of action underlying the anti-tumour activity of these compounds. The immunomodulatory as well as anti-inflammatory activity of I. obscura and/or Ipobscurine was also analyzed.

**Objectives of the study**

- To determine the anti-inflammatory and anti-tumour activity of *I. obscura* methanolic extract.
- To check the effect of *I. obscura* and isolated compound Ipobscurine on immune system of animals.
- To determine the effect of Harmine, *I. obscura* and Ipobscurine on invasion and experimental metastasis.
- To determine the effect of Harmine, *I. obscura* and Ipobscurine on tumour angiogenesis at molecular level.
- To determine the effect of Harmine, *I. obscura* and Ipobscurine on the induction of apoptosis in B16F-10 melanoma cells.