PREFACE
Cancer is a major disease affecting mankind, which is responsible for millions of deaths each year worldwide. Cancer cells are characterized by a failure of cell cycle control which results in their over proliferation (Griffiths et al., 2002). Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells (Kinzler et al., 2002). These abnormalities may be due to the effects of carcinogens such as tobacco, smoke, radiation, chemicals, or infectious agents. Genetic abnormalities found in cancer typically affect two general classes of genes—cancer promoting oncogenes which are typically activated in cancer cells and tumour suppressor genes which are inactivated in cancer cell. The inactivation of tumour suppressor genes results in the loss of normal functions such as accurate DNA replication, control over cell cycle, orientation and adhesion within tissues, and interaction with protective cells of the immune system.

Modulation of immune system by cytotoxic agents is emerging as a major area in pharmacology, especially in cases where undesired immunosuppression is the result of therapy (Geetha et al., 2005). A major drawback of current cancer therapeutic practices such as chemotherapy and radiation therapy is bone marrow suppression resulting in cytopoenia and subsequent suppression of humoral and cellular as well as non-specific and specific cellular responses (Devasagayam and Sainis, 2002). Drug resistance and dose limiting toxicities are the major obstacles for the success of cancer chemotherapy (Ratain and Relling, 2001). Therefore, standard chemotherapy and radiotherapy might reduce the therapeutic benefits obtained by the increased tumour killing of the treatment. Thus combination of chemotherapy or radiotherapy with immunomodulating agents may provide a strategy for overcoming the immunosuppressive effects of chemotherapy or radiotherapy. The modulation of immune response using medicinal plant products as a possible therapeutic measure has become a subject of active scientific investigations (Bhat et al., 2005). Some of the plants and their isolated products with known immunomodulatory activities, *Viscum album* (Kuttan and Kuttan, 1992), *Tinospora cordifolia* (Mathew and Kuttan, 1999), *Withania somnifera* (Davis and Kuttan, 2000), Sulforaphane (Thejass and Kuttan, 2007) *Piper longum* and piperine (Sunila and Kuttan, 2004) have been shown to stimulate the immune system.

Metastasis is the leading cause of cancer related morbidity and mortality. It is the process by which tumour cells disseminate from the primary tumour, migrate
through the basement membrane, survive in the circulatory system, invade into a secondary site, and start to proliferate (Yoshida et al., 2000). Metastasis is the major problem of treatment failure in cancer patients. Matrix metalloproteinases are a family of zinc dependent endoproteinases that are capable of degrading almost all the components of the extracellular matrix and thereby up regulates invasion and metastasis. Among the MMPs reported earlier, MMP-2 and MMP-9 are key enzymes for degrading type IV collagen, which is a major component of the basement membrane (Stetler-stevenson et al., 1996; Chambers and Matrisian, 1997). VEGF has been well described as a cytokine most important for endothelial cell proliferation and the process of angiogenesis which is essential for tumour development. It was previously shown that the gene expression level of VEGF is positively correlated with those of MMP-2 and MMP-9 (Munaut et al., 2003).

Angiogenesis, the development of new blood vessels from the endothelium of a pre-existing vasculature, is a critical process required by most solid tumours to support their localized growth and metastatic dissemination within the host (Griffioen and Molema, 2000; Carmeliet and Jain, 2000). VEGF, a survival factor for endothelial cells by inhibiting apoptosis, is a key angiogenic factor frequently used by tumours and tissues to switch on their angiogenic phenotypes. This potent and unique angiogenic protein stimulates capillary formation, endothelial cell migration and proliferation as well as increases vascular permeability (Ferrara and Davis-Smith, 1997; Nor et al., 1999). The proinflammatory cytokines such as IL-1β, IL-6, TNF-α and GM-CSF act as autocrine growth factors for tumour angiogenesis. These cytokines could be prometastatic or proangiogenic and their deregulated expression directly correlate with the metastatic potential of several human carcinomas (Isner and Asahara, 1993). Moreover altered levels of proinflammatory and proangiogenic factors are observed in various forms of cancer (Chen et al., 1999). Recent studies clearly demonstrated that matrix metallo proteinases (MMPs), a family of Zn dependent endopeptidases that are able to degrade extra cellular matrix (ECM), mediate the release and accumulation of VEGF from the cell matrix (Hiratsuka et al., 2002) and triggers angiogenic switch by rendering VEGF bioavailable to its receptors (Bergers et al., 2000).

Apoptosis or programmed cell death- a series of genetically controlled events that result in removal of unwanted cells- seems to be a reliable marker for the
evaluation of potential agents for cancer prevention. It is involved in maintaining homeostasis in multicellular organisms and any disruption of this process leads to abnormal growth. Defective apoptosis represents a major causative factor in the development and progression of cancer (Kasibhatla and Tseng, 2003). Cancer cells acquire resistance to apoptosis by over expression of antiapoptotic proteins or downregulation or mutation of proapoptotic proteins. During apoptosis cell undergoes certain morphologic alterations include cell shrinkage, plasma and nuclear membrane blebbing, organelle relocalization and compaction, chromatin condensation, and production of membrane-enclosed particles containing intracellular material known as 'apoptotic bodies'. The p53 gene which is strongly implicated in animal and human carcinogenesis is a significant regulator of the process of apoptosis. While apoptotic pathway is related to the induction of p53, this pathway is held in check by the antiapoptotic gene Bcl-2. Induction of apoptosis in cancer cells or malignant tissues is recognized as an efficient strategy for cancer chemotherapy. Thus modulating apoptosis may be useful in the management and therapy or prevention of cancer (Cory and Cory, 2007). In cells undergoing apoptosis there is activation of a family of proteases called caspases which appears to be directly responsible for many of the molecular and structural changes in apoptosis. Caspase-3, an essential member in caspase family, can eventually induce cell apoptosis and be activated by upstream caspases, including caspase-9 and caspase-8. The members of Bcl-2 family play an important role in induction of apoptosis and are considered as a target for anti-cancer therapy. Bcl-2 is an upstream effector molecule in the apoptotic pathway and is identified as a potent suppressor of apoptosis and its down regulation causes tumour regression. On the other hand, predominance of Bax, a proapoptotic protein over Bcl-2 promotes apoptosis (Ray et al., 2010; Kalra et al., 2008).

Activation of transcription factor NF-κB has been linked to apoptosis as it can activate antiapoptotic genes. Upon activation by a variety of stimuli such as carcinogens, inflammatory agents and tumour promoters, NF-κB is translocated to the nucleus where it activate the transcription of target genes which are critical to the establishment of early and late stages of aggressive cancers, including expression of cyclin D1, apoptosis suppressor proteins such as Bcl-2 and Bcl-XL and those required for metastasis and angiogenesis, such as MMPs and VEGF (Bonizzi and
Karin, 2004). Inhibition of deregulated cell cycle progression in cancer cells is an effective strategy to halt tumour growth (Singh et al., 2002).

Medicinal plants are vital sources of new therapeutic drugs. There is a tremendous historical legacy in folklore use of plant preparations in medicine. Scientific studies of plants used in ethnomedicine led to the discovery of many valuable drugs. Natural products have been an important source of chemotherapeutics for many years; more than half of effective cancer drugs can be traced to natural in origins. Development of naturally derived anticancer drugs, therefore, is crucial, and isolation of novel compounds has become an important part of cancer research. Drugs used to treat most cancers are those that can block cell signaling, including growth factor signaling, inflammation, drug resistance, cell cycle, metastasis, angiogenesis and apoptosis. Numerous reports have suggested that plants and their components mediate their effects by modulating several of these recently identified therapeutic targets (Aggarwal et al., 2006; Ma et al., 2009). Terpenoids are minor but ubiquitous components of our diet, and are considered relatively non-toxic to humans. These compounds, therefore, have the potential of being used as cancer chemopreventive agents (Akihisa et al., 2003). In the present study, the effect of Vernonia cinerea and their isolated sesquiterpenoid, Vernolide-A and also other naturally occurring terpenoids such as Perillic acid, Nomilin, and Oleanolic acid on the inhibition of metastasis, and angiogenesis, activation of immune system, and induction of apoptosis are assessed.