Cancer is potentially one of the most dreadful and life-threatening diseases faced by mankind. In most of the developed countries, cancer is the second leading cause of death, and epidemiological evidence points to the emergence of the same trend in developing countries. In today’s world, everyone will be touched by cancer, either as a patient, as a family member or as a friend.

Cancer cells are the descendants of mutated normal cells. As neoplastic cell lineages evolve, they slowly accumulate mutations that enable them in the production of their own mitogenic signals, suppression of contact inhibition and evasion of apoptosis; they metastasize, and even in the case of advanced tumors, construct a vascular system of their own (Leroi et al, 2005). Tumors are heterogeneous both in their morphological and functional aspects. In fact, an individual tumor shows distinct sub areas of proliferation, cell cycle arrest, epithelial differentiation, epithelial to mesenchymal transition (EMT), cell adhesion and dissemination (Brabletz et al, 2005).

Multiple genetic alterations are responsible for the cellular transformation, and a panel of genes has classically been assigned with distinct, independent roles in cancer development, progression and metastasis (Sung et al, 2005). These are classified as oncogenes and tumor suppressor genes. Oncogenes are abnormal forms of normal genes (proto-oncogenes). Tumor suppressor genes are inherent genes that play an important role in cell division and DNA repair; they are critical for detecting inappropriate growth signals in cells.

Uncontrolled cell proliferation and neoplastic growth consistently associate with functional abrogation of different intracellular signaling pathways. Activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway has been found fundamental in transducing extracellular stimuli that modulate
multiple cellular process including cell proliferation, migration and invasion (Roberts and Der, 2007). Transcription factors such as NF-κB, prime mediator of inflammation and Hypoxia inducible Factor, master regulator of tissue oxygen homeostasis play important role in tumor progression. Modulation of their activity via pharmacological or DNA based approaches has potential therapeutic effect (Tripathi and Aggarwal, 2006; Kung et al, 2000).

Apoptosis is a process of cell suicide, the mechanisms of which are encoded in the chromosomes of all nucleated cells. Apoptosis finds relevance in a variety of biologically significant situations that are necessary for the maintenance of homeostasis, and for the normal functioning of the immune system (Kam and Ferch, 2000). The identification of apoptotic triggers is related to tumor evolution also. Apoptosis or programmed cell death is a determining factor, modulating metastasis efficacy. It is regulated by complex molecular signaling systems, and occurs through intrinsic or extrinsic pathways. Modern research has focused on the correlation between apoptosis and cellular proliferation during carcinogenesis. Interestingly, the induction of apoptosis by modulating key apoptotic factors or by inhibiting anti-apoptotic factors is a safeguard system to prevent tumor growth and metastasis (Mehlen and Puisieux, 2006).

The life-threatening aspect of cancer presents itself after the onset of metastasis. Metastasis is defined as the formation of progressively growing secondary tumor foci, at sites discontinuous from the primary lesion. It is associated with poor prognosis, and is an impediment to the development of effective cancer therapies (Welch and Rinker-Schaeffer, 1999). Metastatic transformation is considered to be a process of clonal evolution, wherein, individual cells of the primary tumor progressively acquire new traits, allowing them to invade surrounding tissue, and to migrate to lymph nodes and distant organs (Yokota, 2000). Understanding of the mechanisms of tumor invasiveness, migration and aggressiveness is a future key for improved cancer treatment.
Angiogenesis (angio'gen'esis), the growth of new blood vessels, an important natural process occurring in the body during embryogenesis. In a healthy individual, angiogenesis is carefully regulated through a series of "on" and "off" switches. The situation is reversed in several diseased conditions. In the case of cancer, excessive angiogenesis occurs due to the production of abnormal amounts of angiogenic growth factors, overwhelming the effects of natural angiogenesis inhibitors. In order to progress to a larger size, and to develop metastasis, incipient neoplasia has to develop angiogenic ability. Treatment using drugs that prevent tumor blood vessel formation must be able to constrain secondary tumor development (Kerbel, 2006). Therefore, molecules and growth factors that regulate the tumor specific angiogenesis has become an attractive alternative to targeting tumor cells. (Madhusudan and Harris, 2002).

The outcome of metastasis also depends on the interaction of metastatic cells with tissue environment. The interaction between host and tumor is a dynamic one, and in fact, could be a decisive factor in determining the fate of tumor (Hsu et al, 2005). Tumor associated antigens change continuously over the course of the disease; the tumor cells themselves mutate, and promote tumor progression creating clinical problems. Nevertheless, the ability of the immune system to identify and destroy tumors, and thereby function as a primary defense against cancer, has been known for many years. Recent studies in mouse and human models offer compelling evidence that certain immune cell types, effector molecules, and pathways can sometimes collectively function as extrinsic tumor suppressor mechanisms (Swann and Smyth, 2007).

Modulation of immune response is now being recognized as an alternative to conventional therapy for a variety of diseased conditions, involving the impaired immune response of the host (Upadhaya, 1997). Immunostimulators support T-cell function, including cytotoxic T lymphocyte (CTL), activate macrophages, granulocytes, complement system and natural killer cells, apart from affecting the production of various effector molecules (Wagner et al, 2003). Cytokines, products of
immune cells, form promising agents for the treatment of various human tumors. The largest clinical experience is with interleukine-2 (IL-2) alone or in conjunction with lymphokine-activated killer (LAK) cells. Currently, other cytokines, which enhance the T cells and NK cells, have aroused great interest; phase I and II trials are being conducted in patients with advanced cancer. Indeed, repeated local administration of exogenous cytokines directly into the tumor or into the vicinity of draining lymph nodes appears to promote tumor rejection. Hence, manipulation of immune system becomes an important candidate in cancer therapeutics.

Chemoprevention of cancer is defined as the use of specific natural, synthetic or biological agents, to reverse or to prevent the process of carcinogenesis, thereby preventing the development of cancers. Chemopreventive agents that interact with each stage of carcinogenesis, including initiation, promotion and progression, have been identified. They work by inactivating carcinogens (cancer causing agents) or by activating enzymes, and may act as antioxidants; later, they may inhibit tumor growth by inducing apoptosis.

An array of experimental and clinical investigations has proved that natural products exhibit interesting biological and pharmacological activities, which enable them to be used as chemotherapeutic agents in modern medicine (Verpoorte, 1998). Natural products offer its position in cancer therapeutics as anticancer agents and as immunomodulators. Several plant extracts and isolated compounds have been screened for their efficacy to be used as immunomodulators and anticancer agents; these include Tinospora cordifolia, Piper longum (Mathew and Kuttan, 1999; Sunila and Kuttan, 2004). The plant extracts showed profound anticancer activity without toxicity, suggesting a synergistic activity contributed by multiple constituents present in the whole plant. Moreover, the isolated components of many plants have been turned into anticancer drugs.

Andrographis paniculata has been used for centuries in China, India and Thailand to successfully treat fever, sore throat, herpes, and an array
of other infectious and chronic diseases. *A. paniculata* is used as a wonder drug in traditional Siddha and Ayurvedic systems of medicine, and as a tribal medicine in India and some other countries, for multiple clinical applications. To mention a few, the plant extract exhibits antidiabetic (Zhang and Tan, 2000) and antimalarial activities (Misra et al, 1992). It also reported to possess antihepatotoxic (Trivedi and Rawal, 2000), antithrombogenic (Zhao and Fang, 1991) anti-snake venom, and antipyretic properties, besides its general use in respiratory diseases (Gupta, 2004; Coon and Ernst, 2004; Melchior et al, 2000; Poolsup et al, 2004).

Andrographolide, a bicyclic diterpenoid lactone, is the major constituent of *A. paniculata*. It is a potent hepatoprotective agent (Handa and Sharma, 1990; Kapil et al, 1993), and shows significant anti-HIV activity (Calabrese et al, 2000). Platelets play a key role in the physiological hemostatic process and pathologic thrombosis. Andrographolide has been demonstrated to possess antiplatelet activity and to inhibit platelet activating factor (PAF)-induced human blood platelet aggregation in a dose-dependent manner (Thisoda et al, 2006). In the present study, we have evaluated the immunomodulatory, antimetastatic and antiangiogenic activity of *A. paniculata* and its isolated compound Andrographolide, and the possible mechanism of action at the molecular level.