CHAPTER – 1

INTRODUCTION

Inflammation is a local defensive reaction of host to cellular infection or injury. It is characterized by swelling, heat, redness and pain. Prolonged inflammation can contribute to pathogenesis of several disorders including ulcerative colitis, atherosclerosis, diabetes, neurodegenerative-, cardiovascular- and other life-threatening diseases. Presently, many non-steroidal anti-inflammatory drugs (NSAIDs) are routinely used to treat inflammatory disorders (Chao et al., 2009).

Inflammatory bowel disease (IBD) encompasses chronic inflammatory condition of intestine which includes ulcerative colitis (UC) and Crohn’s disease (CD). The precise mechanism involved in pathogenesis of inflammatory bowel diseases (IBD) remains unknown. However, it has been reported that immune dysfunction plays a decisive role in the development of UC. There is convincing evidence that imbalances between proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), Interferon-γ (IFN-γ), Interleukins IL-1β, IL-6, IL-12 and expression of inflammatory mediators include inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 are believed to play a vital role in modulating the inflammation process. UC is a chronic, relapsing, immunologically mediated and most intractable gastrointestinal disease with high risk of colorectal cancer. Numerous therapeutic
agents for IBD include anti-inflammatory agents and corticosteroids along with certain immunomodulators were used. Although these treatments are effective, they are associated with severe adverse effects such as diarrhea, cramps, abdominal pain accompanied by fever and high blood pressure (Ardizzone & Porro, 2005; Xu et al., 2004).

Chronic inflammation could lead to cellular proliferation – a process that in and of itself increased the risk for aberrant cell proliferation and, ultimately development of malignant cancer. Cancer can be defined as a disease where a group of abnormal cells grows uncontrollably by disregarding the normal mechanism of cell division. Cancer is the leading cause of death worldwide and the WHO (World Health Organization) reported there were 7.6 million deaths (≈ 13% of all deaths) in 2008 and they estimated this will reach up to 13.1 million deaths by the year 2030. During tumorigenesis process, tumor-infiltrating inflammatory cells will produce several cytokines. It has been reported that, pro-inflammatory cytokines including TNF-α, GM-CSF and Interleukins such as IL-1β and IL-6 contribute to carcinogenesis by persuading the survival, growth, proliferation, differentiation and metastasis of cancer cells (Mantovani et al, 2008; Grivennikov et al, 2010).

Immunomodulators are substances that alter the immune response by suppression or stimulation of the immune system. Immunosuppression is associated with an increased susceptibility to infectious diseases and cancer. There are a variety of cancers that is associated with immunosuppression such as cervical cancer, skin cancer and lymphoma. Immunosuppression is also associated with other adverse effects include hypertension, hyperglycemia, dyslipidemia, peptic ulcers, kidney and liver injury (Smith et al., 2003).

The most devastating aspect of cancer is metastasis, which is often resistant to conventional therapies. Tumor cell metastasis is an extremely
complex process and is responsible for as much as 90% of cancer-associated mortality. This multi-step process to occur, cancer cells must migrate from a primary site to the other sites through invasion of surrounding tissues, penetration of the basement membrane of blood vessels (intravasation), enter in to circulation, reattachment to the wound layer of the vascular epithelial cells (extravasation) and finally migrate to specific organs.

In majority of patients with cancer, by the time of diagnosis of the primary tumor, metastasis to the regional lymph node and/or distant organs might have occurred. During this condition, several regulatory pathways are either aberrantly expressed or altered to render tumor cells the ability to successfully accomplish each and all steps of the metastatic process (Hunter et al., 2008). Despite significant advances in the treatment of primary tumors, the development of metastasis remains a continuing therapeutic challenge.

Conventional cancer therapies include radiation and surgery, if the tumor is diagnosed at initial stage and chemotherapy is the treatment of choice for advanced tumors. Although these treatments are effective, it is associated with severe adverse actions include resistance to drug and dose-limiting toxicities such as immunomodulation or immunosuppression. Hence, there is need to develop new therapeutic drugs with minimal toxicity and negligible side effects. Development of drugs from natural sources that prevent or inhibit inflammation and tumor growth by down-regulating select inflammatory mediators has become of keen interest in the field of drug discovery in anti-inflammatory and anti-cancer therapies. Throughout history, plants have been the most consistently successful source of traditional medicines and continue to provide new remedies and to promote human health and well-being. Several traditionally-used medicinal plants and plant products (phytopharmaceuticals) have become potential sources of anti-inflammatory and anti-cancer agents.
Acacia is the second largest genus in the family, *Mimosaceae*, comprising more than 1200 species. Traditional healers in different regions in India have routinely used *Acacia* species for treating inflammation and various cancer of the mouth, bone and skin. Acacia species have been reported to possess a number of biologically active molecules, including flavonoids, alkaloids, tannins, glycosides, phenolics and terpenes. A wide number of pharmacological activities have been found associated with compounds isolated from Acacia species include, anti-microbial, -oxidant, -inflammation and -cancer effects (Lopes et al., 2009). Among the various species of Acacia, *Acacia ferruginea* is a deciduous tree whose products have been used to treat diseases include hemorrhage, leprosy, irritable bowel syndrome and diarrhea (Kirtikar and Basu, 2003). To our knowledge, pharmacological activities of *A. ferruginea* extract are yet to be fully documented. In view of the above findings, we sought to investigate the protective effect of *A. ferruginea* extract against experimental inflammation, ulcerative colitis and tumor models.

The present work could reveal the importance of the *A. ferruginea* extract as potential agent for suppressing inflammation, ulcerative colitis and tumor metastasis. Very few pharmacological studies have reported the beneficial effects of *A. ferruginea*. However, the precise mechanism(s) behind these effects are not well understood. Therefore the present study aims to fill the void in identifying the plausible inflammatory pathways that remain to be explored.
The objectives of the present study are as follows:

i) To investigate the phytochemicals, anti-oxidant and anti-inflammatory activity of *Acacia ferruginea* extract.

ii) To evaluate the protective effect of *Acacia ferruginea* extract against acetic acid induced Ulcerative colitis.

iii) To evaluate the protective effect of *Acacia ferruginea* extract against cyclophosphamide induced immunosuppression and urotoxicity.

iv) To investigate the anti-cancer activity of *Acacia ferruginea* extract against Dalton’s Lymphoma Ascites (DLA) induced tumor models.

v) To investigate the effect of *Acacia ferruginea* extract on inhibition of pulmonary metastasis induced by B16F-10 melanoma cells.