CHAPTER – 1

1. Introduction

1.1 Out Line of Thesis

Cancer can be defined as a disease where a group of abnormal cells grows uncontrollably by disregarding the normal mechanism of cell division. The normal cells that are constantly subject to signals that dictate whether the cell must replicate, differentiate or die. Cancer cells undergoes a degree of autonomy from these signals and normal mechanism results in uncontrolled growth and proliferation and undergoes metastasis (Hesketh, 2012). There are more than 200 different types of cancer. There are over 60 different organs in the body where a cancer can develop from almost any type of cell in the body (Wooster, 2000). Therefore there is usually more than one type of cancer that can develop in any one part of the body. Often though, one type of cancer will be much more common in a particular organ. Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths in 2008 and will be expected to increase till 13.1 million deaths in 2030 (Jemal et al., 2011). Rates are rising as more people live to an old age and as mass lifestyle changes occur in the developing world. The major modalities of cancer treatment to date are surgery, chemotherapy and radiation therapy. The choice of therapy depends upon the location and grade of the tumor and the stage of the disease (Tepper et al., 2008).

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. There are also other adverse effect, such as hypertension, dyslipidemia, hyperglycemia, peptic ulcers, liver and kidney injury (Smith et al., 2003).

Metastasis is a process by which cancer cells spread to other parts of the body through blood circulation and lymphatic system. A tumor formed by metastatic cancer cell is called as metastatic tumor (Klein, 2008). The metastatic process involves tumor cell invasion from the primary tumor, intravasation, arrest and extravasation of the circulatory system to form small tumors known as micrometastasis which stimulate angiogenesis. Tumor cells break away from the primary tumor site and degrade proteins that make up the surrounding extracellular matrix (ECM) that separates tumor from neighboring tissues. Cancer cells degrade the protein, breach the ECM and metastasize to form secondary tumor at distant organs (Nguyen and Massague, 2007).

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease (CD) and ulcerative colitis (UC) (Baumgart and Carding, 2007; Xavier and Podolsky, 2007). Ulcerative colitis characterized by chronic inflammation of the colonic mucosa and submucosa, atrophy and possibly dysplasia limited to the colon. The extent of disease varies and may involve only the rectum, the left side of the colon to the splenic flexure or the entire colon (García Callejo et al., 2005). CD is a chronic, relapsing, transmural inflammation of uncertain etiology that can affect any portion of the digestive tract from mouth to anus, but is predominantly seen in the terminal ileum or colon. The main difference between CD and UC is the location and nature of the inflammatory changes. CD can affect any part of the gastrointestinal tract, from mouth to anus, although a majority of the cases start in the terminal ileum where else UC, in contrast, is restricted to the colon and the rectum (Baumgart and Carding, 2007). Rarely, a definitive diagnosis of neither CD nor UC can be made because of characteristic in the presentation. The CD can be diagnosed by a colonoscopy which is approximately 70%
effective in detecting the disease, with further tests being less effective. Disease in the small bowel is particularly complicated to diagnose, as a traditional colonoscopy allows access to only the colon and lower portions of the small intestines. Introducing a capsule endoscopy helps to diagnosis CD (Pimentel et al., 2000). UC can be diagnosed by complete blood count to check for anemia, thrombocytosis, platelet count, renal function tests, hypomagnesemia and liver function tests to screen for bile duct involvement (Kornbluth and Sachar, 2004).

The major cancer treatments to date are chemotherapy, radiotherapy and surgery (Tepper et al., 2008). Chemotherapy is a potent cytotoxic anti-neoplastic drug which can destroy cancer cells. Moreover they have negative effects ranging from annoying to life threatening such as suppression of the immune system that can result in potentially fatal infections and variety of diseases. Chemotherapy destroys rapidly growing cells like cancer cells, but kills other rapidly growing cells in other parts of the body at the same time (Fidler et al., 2000). Negative effects occur most often in parts of the body where cells divide rapidly. Disadvantages of chemotherapy should be carefully weighed. White blood cells (WBC) fight infection and like other blood cells, have a rapid turnover rate and come under attack during chemotherapy. The decrease in the number of WBC leaves a person vulnerable to infection (Miyahara et al., 2012). The cells that line the stomach and intestines divide rapidly, so gastrointestinal problems occur often as side effects of chemotherapy. Mouth sores frequently occur three to ten days after chemotherapy treatment. Many factors of chemotherapy induce fatigue from anemia, a decrease in red blood cells (RBC) that reduces the oxygen to the body; to stress and anxiety over treatment. Hair loss it one of the common adverse effect of chemotherapy drugs but not life threatening. Chemotherapy can also damage specific organs leads to hepatotoxicity, nephrotoxicity, encephalopathy and cardiotoxicity. Virtually all chemotherapeutic regimens cause suppression of the immune system, often by paralyzing the bone marrow and leading to a leukopenia,
anemia and thrombocytopenia (Joensuu et al., 2008). Radiation and surgery could lower the risk of local recurrence and distant metastases but could possibly obscure the extent of the tumor due to shrinkage and destruction of the margins of the tumor, this may impact the effectiveness of surgery. Therefore, alternative therapeutic approaches are needed for the management of cancer patients.

The approach to treat advanced cancer using natural medicines has drawn much attention recently (Vickers, 2000). Indeed, some natural medicines have been investigated as anti-cancer agents in cancer patients and some encouraging findings have been observed, although objective responses have rarely been found. Such natural medicines have been reported to serve as biological response modifiers by activating, increasing, and or restoring the reactivity of immunological effector mechanisms that are involved in resistance to tumor growth and metastasis (Werner et al., 1996; Wasser et al., 1999). WHO estimated that 80% of the world population in the developing countries mainly relies on traditional medicines for their health care needs, most of them are plant derived (Sheng-Ji, 2001). Plants are the essential and integral part in complementary and alternative medicine and are rich in flavonoids, alkaloids, steroids and phenolic substances that are used to restore health. These substances are claimed to induce paraimmunity, the non specific immunomodulation of essentialy granulocytes, macrophages, natural killer cells and complement function (Sharififar et al., 2009). Because of the conventional medicinal adverse effect, the use of natural plant based products as an alternative to conventional treatment in healing and treating variety of diseases has been in rise (Sharififar et al., 2009). Medicinal plant serves as therapeutic alternative and safer choice with little or no side effects during treatment (Salem, 2005). A wide number of medicinal plants are isolated for their biological constituents that have wider range of medicinal properties. Therefore, in this study our major objective is to investigate on the immunomodulatory efficacy of *Rhizophora apiculata* and its application in inhibiting inflammation, tumor and ulcerative colitis.
1.2 Scope of the study

Mangroves have been less exploited for finding solution in solving human illness. They are rich in active phytochemical constituents and remain unexplored. The present work could reveal the importance of the marine mangrove as a potential immunomodulator, anti-inflammatory and anti-tumour agent. Their role in suppressing the ulcerative colitis has also been investigated in the present study. The present work will shed light in understanding the possible mechanism of action behind this and will encourage the future researchers to look into the phytochemical ingredients and applying it in pharmacology and drug discovery.

1.3 Hypothesis

*R. apiculata* could stimulate the immune system and can be effectively used to decrease the toxic effects of chemotherapeutic drugs. The plant extract could serve as an anti-tumour agent and could suppress the ulcerative colitis in experimental animal models. In order to fulfill the above hypothesis, the following objectives have been formulated.
1.4 The objectives of the present study are as follows

i) To evaluate the phytochemical constituents of *R.apiculata*

ii) To investigate the anti-inflammatory activity of *R.apiculata*

iii) To investigate the immunomodulatory activity of *R.apiculata*

iv) To investigate the anti-tumor and anti-metastatic efficacy of *R.apiculata*

v) To determine the chemoprotective effect of *R.apiculata* against cyclophosphamide (CTX) induced toxicity

vi) To determine the effect of *R.apiculata* against acetic acid induced ulcerative colitis in experimental mice model.