Preface

Cancer is a genetic disease resulting in the loss of normal cell-cycle control, such as unregulated growth and the lack of differentiation. Cancer originates from multiple genetic changes caused by exposure to environmental, dietary and infectious agents as well as other lifestyle factors. Molecular events controlling cell growth and differentiation are complex and involve a complex array of signaling factors and the intracellular pathways mediated by them. Changes in such pathways and/or signal molecules may cause the uncontrolled growth in cancer. Cancer cells share a number of characteristics including self dependence on positive regulatory signals; lack of response to growth inhibitory signals, limitless proliferation, resistance to apoptosis, capability of getting nutrients and oxygen by angiogenesis, and the ability to invade and establish distal metastasis (Hanahan and Weinberg, 2000). The burden of cancer is increasing in economically developing countries as a result of population aging and growth, environmental pollution, infections as well as, adoption of cancer-associated lifestyle choices including smoking and physical inactivity. At the same time the toxicities associated with the present cancer modalities, radiation and chemotherapy also makes the cancer treatment and resistance to antineoplastic drugs had made the researchers for seeking new sources of natural chemopreventive agents with low toxicities. The search for potential anticancer agents from natural products dates back to centuries. Many plant products have proven to be an important source of anticancer drugs (Cragg and Newman, 2005). A number of mechanisms exist by which phytochemicals aid in the prevention of cancer. These mechanisms include antioxidant or free radical scavenging, anti-inflammatory activities and induction of apoptosis.

The generation of excessive reactive oxygen species (ROS) as byproducts of aerobic metabolism and a concomitant fall in the intrinsic antioxidant capacity of cells leads to a state of oxidative stress, which contributes to carcinogenesis. High levels of ROS generated by external stimuli including chemical carcinogens, ultraviolet radiation, bacterial or viral infection, etc. elicit deleterious effects on human health (Surh et al. 2005). ROS, such as superoxide radical anion, hydroperoxyl radical, hydrogen peroxide, and hydroxyl radical, contribute to tumorigenesis either directly by damaging critical biomolecules or indirectly by modulating cellular signal transduction pathways (Kundu and Surh 2008). Moreover, accumulation of ROS in vivo leads to a state of persistent local inflammation. Inflammation plays a role in
multistage carcinogenesis by several distinct mechanisms including damage of genomic DNA and alteration of intracellular signal transduction leading to abnormal cellular growth. Thus, both oxidative stress and inflammation not only initiate tumorigenesis but also promote the proliferation of damaged cells and create a tumor microenvironment favorable for the neoplastic transformation of premalignant cells (Kundu and Surh 2008; Surh et al. 2005).

Cancer is now being the major cause of death around the world despite of global efforts. Currently, there are three principal ways of treating cancer, surgery, radiotherapy and chemotherapy. Surgery and radiotherapy are frequently used as first-line therapy in treating primary cancers. Chemotherapeutical drugs alone or in combination with other additional treatments are also used to cure cancer. These chemotherapeutic agents includes various chemical and synthetic compounds with potential anticancer activity was identified including alkylating agents (Cyclophosphamide, Cisplatin etc); anthracyclines (Doxorubicin, Daunorubicin), antimetabolites (methotrexate, 5-fluoro uracil, 6-mercaptopurine) etc. However, more effective anticancer therapies are required for most patients to achieve a complete eradication of the disease. And all these categories of antineoplastic agents were of profound side effects and hence the drug dose, which can be used for cancer therapy, is limited by the normal tissue tolerance. Indeed, most existing anticancer agents target DNA replication of dividing cells, thus inhibiting tumour cell growth but also normal cell growth. This causes many undesired side effects such as nausea and vomiting, alopecia, mucositis, myelosuppression and reproductive sterility. These side effects of chemotherapy can have a devastating impact on a patient’s quality of life (Pasetto et al. 2007). Thus cancer prevention has become an integral part of cancer control. An extremely promising strategy for cancer prevention today is chemoprevention, the use of synthetic or natural agents to block the development of cancer in humans (Bertram 2000). The promising results from numerous preclinical and limited clinical studies also highlight the chemoprevention strategy as a realistic approach to fight cancer (Kundu et al. 2008; Surh 2003).

The chemoprotective agents are classified by which they are effective in preventing the formation and absorption of carcinogenesis (initiation) or as blocking agents that prevent the carcinogens from reaching or reacting with the cellular targets by increasing detoxification or by trapping reactive carcinogenic species. Mechanistically, chemoprevention can be achieved by enhancing cellular antioxidant
and detoxification capacity, promoting carcinogen detoxification, suppressing abnormally activated pro-inflammatory signaling pathways, down-regulating expression of proteins involved in cell proliferation, inducing apoptosis of precancerous or malignant cells, and inhibiting neovascularization (Kundu et al. 2008). So chemoprevention, by definition, is the use of agents to slow the progression of, reverse, or inhibit carcinogenesis, thereby lowering the risk of developing invasive or clinically significant disease (Kelloff et al, 2001). Consequently, an effective chemopreventive agent should intervene early in the process of carcinogenesis to eliminate premalignant cells before they become malignant (Kakizoe, 2003).

The natural world once served as the source of all medicinal agents, and plants provided most of these therapeutic entities. Documentation found in archeological excavations proves that various medicines extracted from plants were used as long ago as 2500 BC (Wang, 2008). Medicinal plants have always had an important place in the therapeutic armory of mankind. Up to 80% of populations in developing countries are totally dependent on plants for their primary health care. And despite the remarkable progress in synthetic organic chemistry of the twentieth century, over 25% of prescribed medicines in industrialized countries derive directly or indirectly from plants (Newman et al., 2000). At present, there is a general consensus that plant polyphenols, flavonoids, catechins, and lignans are the key constituents in cancer prevention (Kinghorn et al. 2003, 2004). In addition, a large proportion of the now conventional anticancer drugs are derived from natural sources, e.g. Vincristine and Vinblastine from *Catharanthus roseus*, Paclitaxel and Docetaxel from *Taxus* species, the podophyllotoxin derivatives Etoposide and Teniposide from *Podophyllum* species, Camptothecin and its semisynthetic derivatives Irinotecan and Topotecan from *Camptotheca acuminata*. A recent estimate stated that approximately 60% of drugs in clinical trials for the multiplicity of cancers are either natural products, compounds derived from natural products, or drugs containing pharmacophores derived from natural products (Cragg and Newman 2000).

Since, the plant kingdom has historically been a major source of bioactive compounds for medicine, food additives, pigments, insecticides, cosmetics and fine chemicals. Unfortunately, their supply by the extraction from natural plants resources has some difficult issues: limited quantity of active metabolites in the plant, low plant growth rate, limited localization of active ingredients in the specific organs, and
destruction of the natural resources. In comparison with the conventional cultivation, plant cell and tissue cultures are sustainable alternatives to the whole plant with clear advantages. They are independent of geographical and seasonal variations and environmental factors, ensure the continuous supply with uniform quality and yield, and provide efficient downstream recovery and product. Successful strategies have also been adopted to enhance the secondary metabolites in plant cell culture, including screening and selection of highly productive cell lines, addition of precursors, manipulation of nutrients to improve yield, optimizing the culture environment, and challenging by compounds of pathogenic origin as elicitors (Rao and Ravishankar 2002). With optimized conditions, several plant metabolites are accumulated in plant cell culture even at higher level than found in intact plants.

The present study is aimed to evaluate the biological activities of *Hibiscus furcatus* flower, leaf and root bark extracts. This work mainly concentrated on the antioxidant, anti-inflammatory, antitumor using in vitro and in vivo models, and also the capability of these extracts in protecting mice from radiation and other chemotherapeutic drug induced damages. *H. furcatus* (*Family: Malvaceae*) is distributed throughout India, common in the Western Ghats and plains, usually straggling extensively our forest thickets or hedges and bushes in the waste land in plains. Flowering is from November to February. This plant is used as medicine in folklore medicine, the leaves are sour and considered to be astringent, anti-inflammatory and antihelmetic, and are useful in the treatment of eye diseases. The roots are cooling, diuretic and anti-inflammatory and are used in the treatment of diseases of urinary tracts. It is also used for cleaning kidneys (Sivarajan and Balachandran, 1994). The previous phytochemicals present in *H. furcatus* revealed that the leaf petroleum ether contains freidelin, taraxerol, β-sitosterol. The flowers are reported for the presence of gossypirin, gossypin and hibiscatin (Bindu et al., 1997; Nair et al, 1981).

In addition, the presence of an antitumor alkaloid, camptothecin and its natural derivative 10- Hydroxy camptothecinin *Ophiorrhiza incarnata* and its regeneration by tissue culture method were also studied. *O. incarnata* is herbaceous plant distributed in southern Western Ghats, in kerala. Few species of the genus *Ophiorrhiza* (*Family Rubiaceae*) has been reported for the presence of camptothecin (Wall and Wani, 1998) a well-known monoterpenoid indole alkaloid possessing remarkable antitumor activity and at present, two semi-synthetic camptothecins, topotecan and irinotecan,
are used clinically as antitumor agents. Like other species of *Ophiorrizha*; *O. incarnata* may contain the antitumor compound camptothecin.