1.1 Introduction

Cancer arises due to extensive genetic instability accumulating in tumor genomes over years making it difficult to treat, leading to high morbidity and mortality. According to the International Agency for Research on Cancer, in 2012, 8.2 million people died of cancer across the globe. In India alone, 682,830 deaths occurred due to cancer with solid tumors of breast, lung and colon accounting for about 26.7% of total cancer deaths (Ferlay et al, 2013). Cancer is a progressive disease characterized by uncontrolled cell growth, tissue invasion and metastasis. Cancer cell genotype is a manifestation of six essential alterations in normal cell physiology; self sufficiency of growth signals, evasion of apoptosis, limitless replication, angiogenesis, tissue invasion and metastasis (Hanahan and Weinberg, 2000). Western medicine offers a range of therapies for cancer including chemotherapy, radiation and surgery; however, they are very expensive and are associated with serious side effects and morbidity. An alternative solution to Western medicine is the use of plant-derived products which are low-cost and can be used alone or as adjuncts to enhance therapeutic effects and minimize toxicity.

Plants have a long history of use in the treatment of cancer. Hartwell, in his review of plants used against cancer, lists more than 3000 plant species that have reportedly been used in the treatment of cancer (Cragg and Newmann, 2005; Hartwell, 1982). Nature has provided effective anticancer agents in current use, which include drugs of microbial origin such as doxorubicin, dactomycin, bleomycin and a number of plant-derived drugs like taxol (paclitaxel), taxotere (docetaxel), vincristine, etoposide, topotecan and irinotecan (Mukherjee et al, 2001). Indeed, molecules derived from these natural sources have played, and continue to play, a dominant role in the discovery of leads for the development of conventional drugs for the treatment of cancer (Cragg and Newmann, 2005).

Cancer cells modulate multiple signaling pathways to prevail and plant products are known to modulate multiple pathways simultaneously. An improved understanding of the signal transduction pathways and their roles in cancer suggest that simultaneous inhibition of multiple targets may optimize the therapeutic benefit. With advanced knowledge of isolation techniques and molecular biology, various plants have been identified as anti-cancer agents and their mechanism of action has been elucidated. There are a number of chemotherapeutic, immuno-modulating agents and cytotoxic drugs in Western medicine which are very expensive and have serious adverse effects and
morbidity associated with them. Accordingly, there is a considerable interest in the development of novel, safe, low-cost anti-cancer agents from natural sources inclusive of plant secondary metabolites, which modulate multiple biochemical pathways in cancer cells simultaneously.

Plant secondary metabolites continue to play an important role in cancer therapeutics. Over 200 natural-product-derived compounds are currently undergoing clinical trials and at least 80 such products are in the preclinical and clinical phase developmental stages for cancer (Harvey 2008). Between 1981 and 2002, 48 out of 65 drugs approved for cancer treatment were natural products, based on natural products, or mimicked natural products in one form or another (Agarwal et al, 2006). Natural products have provided us numerous lead compounds against cancer and there is a growing trend for the development of natural product-like libraries which are low-cost, safe, have the ability to target multiple pathways and selective to cancer cells with minimal toxicity to normal cells. The Indian sub-continent has great botanical diversity and widespread use of traditional systems of medicine, however, a small number of plants have been evaluated scientifically for their potential clinical benefit. Still, there is a lot of untapped therapeutic potential in folkloric medicine which needs to be investigated. Compounds of natural origin have often provided new leads for anti-cancer agents in use. Of the 121 prescription drugs in use for cancer treatment, 74% are derived from plants (Agarwal et al, 2006). Plant-derived agents act by modulating various signaling pathways in cancer cells. Some of the molecular targets for plant-derived drugs are NF-κB, p53, Activated protein-1, JAK-STAT pathway, Ras, cell cycle mediators (CDKs and cyclins), apoptosis-related proteins (Bax, Bcl-2, Caspases, FLIP, Survivin, IAPs), angiogenesis (VEGF), invasion and metastasis regulators (MMP-9, ICAM-1). Plant-products are known to modulate multiple signaling pathways simultaneously; hence they can be very effective in inhibiting uncontrolled cell proliferation of cancer cells which have multiple survival strategies. Many plant-derived agents such as curcumin, diallyl disulfide, lupeol, theaflavins are known to activate p53, cell cycle arrest and apoptosis (Mondal et al, 2006).

Apoptosis and cell cycle arrest are the mainstays for cancer treatment; an important mode of action for many anti-cancer therapies. The two main pathways of apoptosis are extrinsic and intrinsic pathways. Each pathway requires specific triggering signals to begin an energy-dependent cascade of molecular events. Each pathway
activates its own initiator caspase (8 and 9 respectively) which in turn activates the executioner caspase-3 (Elmore, 2007). Hence, the expression of caspases can be assessed to determine the mode of action of action of cell death. The development of novel cancer therapeutics is targeted towards cell cycle and apoptosis pathways which would be effective in checking uncontrolled cellular proliferation of cancer cells. Wild type p53 acts in response to a wide range of cellular stresses and performs its most important biological functions in response to DNA damage - cell cycle arrest or apoptosis. Following DNA damage, a cell can arrest its progression through the cell cycle. p53 is involved with cell cycle delays in G1, G2 and mitotic spindle check-point. However, the G1/S arrest is widely observed in accordance with the wild-type p53 status of the cells (Amundson et al, 1998).

p53 activation can also facilitate apoptosis by the extrinsic death receptor pathway and intrinsic mitochondrial pathway. The p53 protein activates the “death” receptors (belonging to the TNF-R family) and caspase 8 directly - components of extrinsic apoptotic pathway. The intrinsic mitochondrial pathway comprises of the Bcl-2 family of proteins that regulate the mitochondrial membrane permeability and can be either pro-apoptotic or anti-apoptotic. Bax is a pro-apoptotic member of the Bcl-2 family while Bcl-2 is anti-apoptotic; hence a balance between these proteins is important for cell survival (Elmore et al, 2007). Apoptosis is one of the mainstays for cancer treatment; hence, the development of novel cancer therapeutics is targeted towards these pathways which would be effective in checking malignant cells. Activation of p53 pathway is a leading target for new cancer drug development. Mutations that inactivate the p53 gene pathway activation are common occurrences in human cancers which deregulate cell cycle and apoptotic downstream pathways (Hwang et al, 2007).

There are a number of plants which have not been investigated for their potential therapeutic benefits. The present work encompasses the evaluation of the anti-cancer potential of two medicinal plants; Memecylon umbellatum and Nardostachys jatamansi which have been used in traditional medicine for a number of ailments including inflammatory conditions and cancer.

The leaves of Memecylon umbellatum have been used to treat various infections and inflammatory conditions (The Wealth of India, Rajakumar et al, 2009, Majumdar et al, 2009, Song and Kim, 2011). In a comprehensive screening of plants for pharmacological activities, M. umbellatum showed anti-cancer activity against Lewis
lung carcinoma in mice (Dhar et al, 1968) and cytotoxic activity in brine shrimp lethality assay (Rumzhum et al, 2012). Active constituents such as umbelactone, β-amyrin, sitosterol, ursolic acid and sitosterol-β-D-glucoside have been isolated from the plant (Agarwal and Rastogi, 1978), however, no further anti-cancer studies have been carried out for this plant.

_Nardostachys jatamansi_ is used traditionally for treatment of various types of cancer as reported by Hartwell (Hartwell, 1982). It is also used in traditional Thai medicine for treating cancer (Saetung et al, 2005). The active constituents include sesquiterpenoids and alkaloids (Medicinal plants of India, 1987). In recent preliminary studies, the plant was found to possess cytotoxicity against lung and prostate cancer cells (Saetung et al, 2005). However, further systematic studies are requisite to explore the anti-cancer activity of the plant. _M. umbellatum_ and _N. jatamansi_ are two medicinal plants which can add to the armamentarium of plant-derived products against cancer. Hence, these plants need to be investigated systematically for their anti-cancer activity and identify the phytochemical basis of their action.

Hence, the present work encompasses the investigation of these two plants; _M. umbellatum_ and _N. jatamansi_ for their anti-cancer activity and identifies the phytochemical basis of their action. The approach of bioactivity guided fractionation for identifying phytoconstituents with potential anticancer activity in 4 cancer cell lines which express wild type p53 – A-549 (lung carcinoma), MCF-7 (ER positive breast adenocarcinoma), MDA-MB-231 (ER negative metastatic breast carcinoma) and HCT-116 (colon carcinoma) cells (O’Connor, 1997) was used. An attempt was made to delineate the downstream signaling evoked by the isolated phytoconstituents and their effects on apoptosis cascade (extrinsic and intrinsic) and cell cycle checkpoints.

1.2 References


Hartwell JL. Plants used against cancer. Quaterman, Lawrence, MA, 1982; 654-656.


Medicinal plants of India. Vol.2. ICMR publications, New Delhi, 1987; 312-323.


