ABSTRACT

Cancer has been recognized as the second most common cause of death in the world. A cancer can be defined as a new growth (neoplasm or tumour) resulting from the continuous proliferation of abnormal cells. The vast catalog of cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth: self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. Each of these physiologic changes - novel capabilities acquired during tumour development - represents the successful breaching of an anticancer defense mechanism hardwired into cells and tissues.

Plant products and their modified analogs have been rich sources of clinically useful drugs, including anticancer agents. Several plant-derived drugs are presently in use in pharmaceutical care as exemplified paclitaxel, vincristine, vinorelbine, teniposide and various water soluble analogs of camptothecin. There is however a need for new drugs to treat the increasing number of patients with different cancers. Traditional medicines of different countries have been used for the treatment of several diseases including cancers. The knowledge in traditional medicine for treatment of diseases needs to be understood from the view of modern sciences. The approach involved use of conventional solvent extraction procedures, and monitoring bioactivity on HEp-2 cell line, a laryngeal carcinoma cell line. At each step of the process the different fractions isolated were tested for specific anti-proliferative activity by measuring the inhibition of $[^3H]$ thymidine incorporation, lactate dehydrogenase release and trypan blue exclusion assays. The ethyl acetate
fraction that contained the bioactivity was further purified by a preparative column. The purity of each of the fractions and its bioactivity was checked on thin layer chromatography plates. Fraction that demonstrated a single compound and showed maximum anti-proliferative activity was taken for structure analysis. The structure of the lead compound was elucidated using NMR and mass spectrometry analysis. Apoptosis or programmed cell death is a highly organized physiological mechanism to destroy injured or abnormal cells. A successful anti-cancer drug should kill or incapacitate cancer cells without causing excessive damage to normal cells. This ideal situation is achievable by inducing apoptosis in cancer cells. The bioactivity based screens used in this study involves measuring proliferation of cells using $[^3H]$Thymidine and monitoring known index of apoptosis as a first step to understand whether both pure and crude compound activate signal transduction cascade in driving the cells towards apoptosis, namely Telomerase, IFN-γ, TNF-α, iNOS, death receptors, p53, bcl2, bax and caspase 8 at a second level, with a view to postulate the possible mechanism by which these extracts induce cell death.

Signal transduction therapeutics is now a dominant theme of drug discovery and has a major impact in cancer therapeutics.

A great variety of natural products are used as anti-cancer agents, their anti-mitotic activity being due to their interaction with microtubular protein. Taxol is an important new cancer chemotherapeutic agent that is effective in the treatment of many types of cancer. The principal chemotherapeutic target of taxol is microtubules. Because telomerase activity is detected in almost all advanced tumours, it is hoped that scientists may be able to develop a therapy that inhibits telomerase activity and interferes with the growth of many types of cancer. Following conventional treatments (surgery, radiotherapy and chemotherapy) anti-telomerase agents would most likely be given to limit the proliferative capacity of the rare surviving tumour cells in the hope that this
would prevent cancer recurrence. In addition, telomerase inhibitors could also be used as chemopreventive agents in high cancer-susceptibility individuals or in early stage cancer to prevent overgrowth of metastatic cells.

Bioassay-guided fractionation of *P. urinaria* has enabled us to obtain a pure compound with proven anti-cancer activity. Its molecular structure was elucidated as 7'-hydroxy-3',4',5,9,9'-pentamethoxy-3,4-methylenedioxy lignan. To be brief, our studies highlight the ability of integrating ethanobotanical leads aided with chemical isolation techniques, and studying various aspects of apoptotic cell signaling cascades and to isolate molecules with potent anti-cancer activity. This study also indicates that this pure compound and crude ethyl acetate extract induces apoptosis in a broad spectrum of cancerous cell lines and block known anti-apoptotic (*bcl-2*) and stimulate proapoptotic (*bax*) cascades. Inhibition of telomerase activity, enhanced polymerization of tubulin, activation of IFN-γ and iNOS were observed and also we have found the activation of pro caspase 8 which in turn activates Caspase 3, significance of which in apoptosis is well known.

From *A. marmelos*, an anti-proliferative agent, 9-hydroxyl-7H-furo-[3,2,9] [1]-benzopyran-7-one was isolated and by using simple *in vitro* screens, it was found to exhibit anti-proliferative activity in a wide range of cancerous cell lines. The schematic events in apoptosis were analysed in detail, using HEp-2 cell line as a model. In that particular study we have found that both pure compound and crude ethyl acetate extract were capable of inducing apoptosis through inhibition of telomerase, enhanced polymerization of tubulin, p53 activation, activation of IFN-γ and iNOS which altogether ensues in the suppression of NF-kB. Activation of TNFα, TNFR1, in turn activates TRADD, caspase 8 and caspase 3. These communal actions drive the cell in concert, into the apoptotic phase.