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Review Article

Indian Medicinal Plants: An Emerging Complementary Adjuvant Therapy for Cancer Treatment

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Abstract

Cancer being one of the distressing diseases requires special consideration with respect to therapeutics. Despite the availability of a number of chemotherapeutic drugs, vast majority of cancer cases relapse which might be due to the development of drug resistance. Moreover, these chemotherapeutics possess severe side effects and are expensive. Taken these drawbacks of chemotherapeutics into account, an emerging role of traditional Indian medicinal system has been studied and evaluated in a variety of tumors ranging from solid tumors to haematological malignancies. Several such medicinal plants such as curcumin, cinnamon, ashwagandha, ginger, long pepper, etc have shown promising anti-tumor effect alone or as adjuvant chemotherapy. Furthermore, the effect of these medicinal plants on drug resistant tumor cells have also been investigated and found that the proteins up regulated while development of drug resistance such as P-glycoprotein have been suppressed by these medicinal plants suggesting their chemo-sensitizing role in treatment of cancer.

Keywords: Cancer; Indian medicinal system; Cinnamon; Curcumin; Ginger; Long pepper; Ashwagandha

Introduction

Cancer is one of the distressing diseases globally affecting a considerable number of people. According to the National Cancer Registry Programme of the India Council of Medical Research (ICMR), more than 1300 Indians die every day due to cancer. The mortality rate due to cancer has been increased by approximately 6% between 2012 and 2014. As per Population Cancer Registry of ICMR, the incidence and mortality of cancer is highest in the North Eastern region of the country [1]. A variety of chemotherapeutic drugs (either cytotoxic or immunomodulatory) are currently employed for the treatment of cancers ranging from solid tumors to haematological malignancies but besides being tremendously expensive, these drugs are associated with serious side effects, morbidity and lack of effectiveness [2,3]. Furthermore, frequent failure in chemotherapy leading to relapse necessitates the identification of efficient, cost-effective treatment regimen with minimal side effects.

The plausible cause of cancer recurrence could be the drug resistance or involvement of multiple pathways for the development and progression of cancer. Therefore, in order to overcome these difficulties, utilisation of traditional system of medicine for the treatment of cancer is the main focus of research. However, some of the widely used anticancer drugs, such as taxol and vinca alkaloids, are obtained from medicinal plants. Thus, this review focuses on certain traditional Indian medicines in context with the improved cancer treatment. Ayurveda and Unani systems, the major traditional forms of medical practice in India, have given many useful leads in developing medications for chronic diseases. Being derived from the natural sources, these chemo-preventive agents are considered pharmacologically safe. The current review, although brief, evaluates the untapped therapeutic potential of these agents in the setting of several molecular targets for the treatment of cancer [4].

Cinnamon

Our lab has previously reported the anti-cancer property of Cinnamon Bark Powder Extract (CBPE or dal-chini), an extract of Ayurvedic-Unani origin in Multiple Myeloma (MM) [5]. CBPE (at IC50: 72µg/ml) has shown cytotoxic as well as cytostatic property against myeloma cells (RPMI8226) as exemplified by increase in sub-G1 phase and decrease in G2/M phase in propidium iodide staining on 48hrs and 72hrs (Figure 1). The effect of cinnamon extract has been investigated on angiogenesis, one of the important hallmarks of cancer. We have observed significant reduction in angiogenic factors such as VEGF, HGF, Angiopoietin-1 and Angiopoietin-2 both at mRNA and protein level as assessed by Q-PCR and western blotting respectively (Figure 2). In addition, the inhibition of cyclooxygenase (COX)-1 and 2 has been observed upon treatment of CBPE in myeloma cells (Figure 3) affirming the anti-myeloma effect of cinnamon extract along with the correlation between angiogenesis and cyclooxygenase which could be studied further for the purpose of therapeutics in MM. This extract could also be studied in combination with currently used chemotherapeutic drugs (such as lenalidomide or bortezomib) to explore its potential as an alternate and complementary therapy for the malignancy.

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Other reports have also accounted the concordance findings. 50-70μM cinnamon extract caused growth inhibition of K562 leukemic cells by arresting the cells at the G1 stage and significantly increased the apoptosis rate. Cinnamon extract treatment also showed up regulation of erythroid and myeloid differentiation antigens while down regulation of megakaryocytic differentiation antigens in a dose-dependent manner by investigating antigenic variation of cell surface markers. Hence, Guan et al. [6] suggested the effectiveness of cinnamon extract for the treatment of leukemia. Zhang et al. [7] also reported the suppression of VEGF expression, blood vessel formation, and tumor growth in a human ovarian tumor model in mice treated orally with 0.3mg/g cinnamon extract suspension. These findings support the notion that cinnamon could be effectively used for cancer therapeutics in future with the necessisity of further investigations.

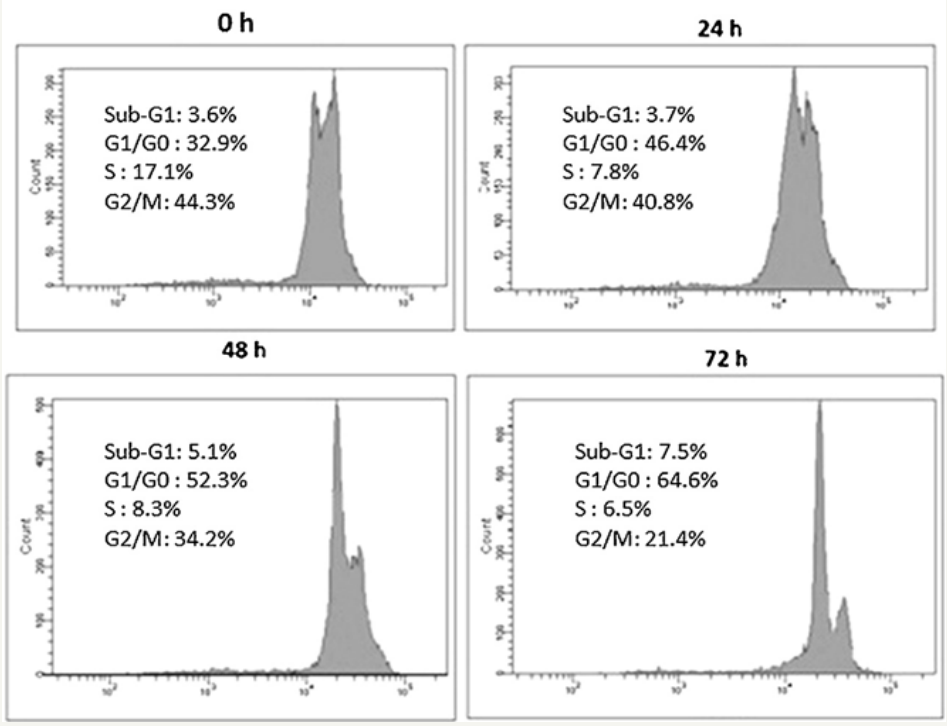

Figure 1: Histograms showing propidium iodide staining of DNA content, with the x-axis reflecting fluorescence intensity and the y-axis the cell number. Flow cytometric determination of cell cycle distribution of RPMI8226 cells following 24h, 48h and 72h of treatment (adapted from Khan et al. [5])

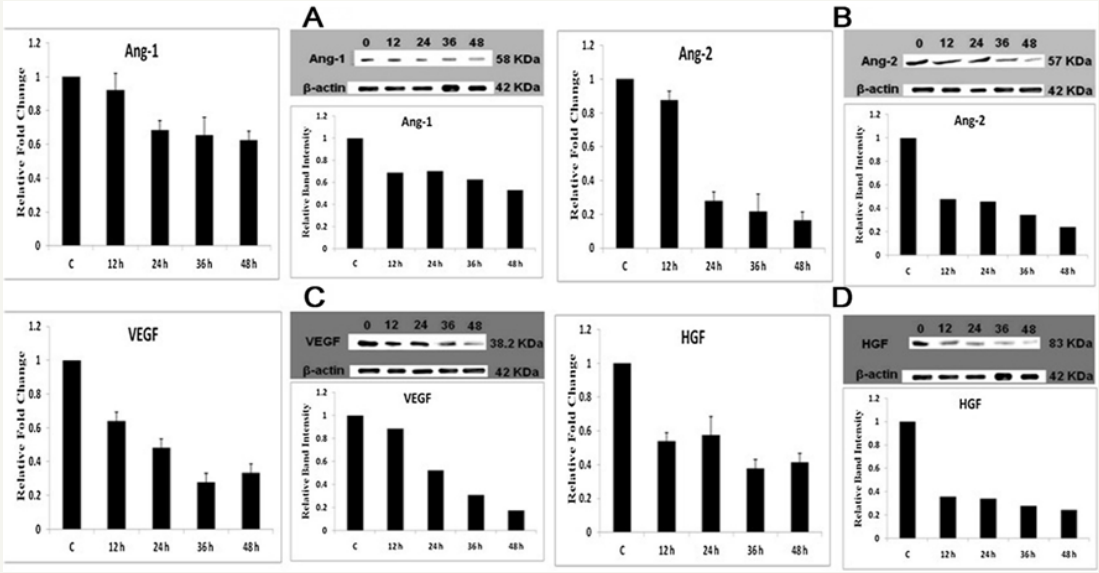

Figure 2: Effect of treatment of CBPE on mRNA (Left Panel) and protein (Right Panel) levels of angiogenic factors in a time dependent manner. (A): Angiopoietin 1 (Ang-1); (B) Angiopoietin 2 (Ang-2); (C): vascular endothelial growth factor (VEGF); (D): hepatocyte growth factor (HGF) (adapted from Khan et al. [5]).

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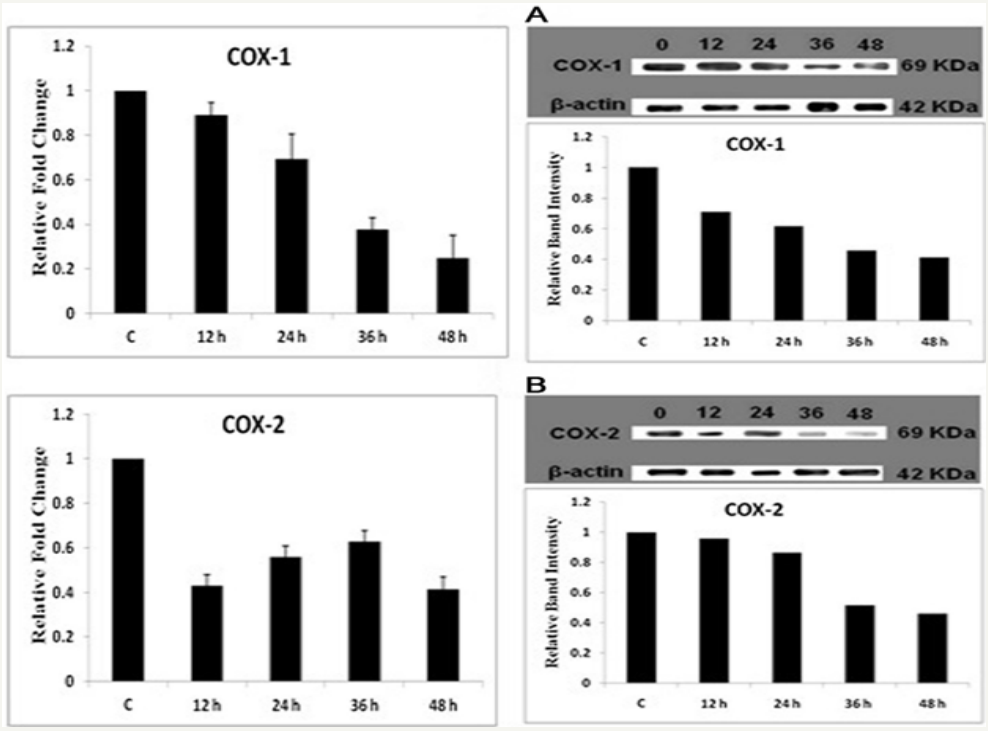

Figure 3: Effect of treatment of CBPE on mRNA (Left Panel) and protein (Right Panel) levels of cyclooxygenase in a time dependent manner. (A): Cyclooxygenase 1 (COX-1); (B) cyclooxygenase 2 (COX-2) (adapted from Khan et al. [5]).

Ginger

The natural herbs contain numerous active components which are likely to target multiple mechanisms would be beneficial for multiple targeted therapies for better treatment of cancer [8]. Ginger (*Zingiber officinale*), has been used for centuries in Indian traditional medicine system as an anti-inflammatory and antiemetic agent. Ginger or its active chemical component are capable of inducing a potent chemo-sensitizing effect which is the ability of a low concentration of herbal extract or its active component capable of reversing anticancer drug resistance when combined with a particular anticancer drug for which the cancer cells have developed resistance. Some resistant cancer cells such as MES-SA/Dx-5, doxorubicin-resistant sarcoma cells have shown the over-expression of P-glycoprotein, an efflux pump capable of pumping the active drug from intracellular site to extracellular site and thus decrease drug intracellular concentration. 6-Gingerol (6G), the active principle of ginger root at 20μM concentration has shown the suppression of P-glycoprotein transporter along with the reduction in ROS production in these resistant cells contributing to revert chemo-resistance [9]. Therefore, alone or combination of ginger extract along with chemotherapeutic drugs such as doxorubicin has shown heightened response against breast carcinoma and acute monocytic leukemic cells [10,11].

The effects of ginger extract on tumor xenograft mice model affims its anti-cancer potential. 6-Gingerol, present in the pungent extracts of ginger was given intraperitoneally in HeLa cervical cancer xenograft cells at 2.5mg/kg and 5mg/kg body weight. Treatment with 6G induced significant reduction of tumor volume, tumor weight, proteasome inhibition and p53 accumulation in vivo. The 6G treatment was devoid of any toxic effects as it did not affect body weights, hematological and osteogenic parameters [12]. Thus, cumulatively, these literatures emphasize the therapeutic and chemo-sensitizing effects of ginger in the management and better treatment of variety of cancers.

Curcumin

There are plethoras of such natural medicinal plants tested for the anti-tumor potential in several malignancies. Curcumin (turmeric), an active constituent of *Curcuma longa* has shown synergistic effect in combination with radiation therapy or chemotherapy in cancers including cervical carcinoma and leukemia [13]. Recently, this Indian spice has shown potent inhibition of growth of non-small cell lung carcinoma cells in vitro via inducing both apoptosis and autophagy suggesting its probable use as candidate therapeutics in human lung carcinoma [14]. Besides the anti-tumor role of curcumin in solid tumors, it has also been reported to suppress the proliferation of chronic myelogenous leukemic cells [15]. Apart from the effect in vitro, several in vivo studies also underscore the anti-tumor potential of curcumin. Treatment of orthotopic esophageal squamous cell carcinoma bearing mice with 50mg/kg curcumin or 50mg/kg SSC-5 intraperitoneally resulted in an inhibition in tumor growth and invasion [16]. Similar findings were reported for anti-tumor property of curcumin in colon carcinoma and chronic myelogenous leukemic xenograft models in vivo [17,18].

Ashwagandha

Ashwagandha (*Withania somnifera*) is considered to be one of the important medicinal herb of several traditional systems of medicine, such as Ayurveda, Unani, and Siddha. It had been used for

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millennia as a Rasayana for its wide ranging health benefits. Yadav et al. [19] reported the anti-cancer property of root, stem and leaves of ashwagandha against human cancer cell lines. Ashwagandha root extract showed dose-dependent inhibition of breast tumor growth and metastatic lung nodule formation with minimal systemic toxicity [20]. The root extract also found to have chemopreventive effect against fore stomach and skin cancer [21]. Apart from reports in solid tumors, there is only a single report of ashwagandha plant extract in hematological malignancy in which DMSO extract obtained from roots of ashwagandha showed cytostatic and cytotoxic activity against human T-lymphoblastoid cell line [22]. In addition, the anti-tumor property of one of the components of ashwagandha, i.e., With aferin A has also been assessed in various cancers [23,24]. Moreover, intraperitoneal injection of 2mg/kg with aferin A significantly reduced the tumor volume in colon carcinoma xenograft model [25]. These results affirm the plausible role of ashwagandha for better cancer therapeutics in future.

Long pepper

Long pepper (*Piper longum*) has also gained importance in concordance with the anti-tumor potential against a range of tumors. Hang et al. [26] has recently reported the induction of cell death in head and neck squamous cell carcinoma upon treatment with different doses (5μM and 10μM) of piperlongumine, an alkaloid identified in piper longum. Han et al. [27] has also reported the chemosensitizing effect of long pepper by reverting cancer drug resistance. They have observed that co-treatment of Piperine (an alkaloid from long pepper) at 20μM and mitomycin-C (a chemotherapeutic drug) at lower concentration of 0.025μg/ml resulted in a synergistic suppression of cell proliferation and induction of apoptosis in mitomycin-C resistant cervical cancer cells. They have proposed a novel therapeutic strategy of utilization of piperine to potentiate mitomycin-C induced anti-tumor effect on cervical cancer cells with drug resistance through blocking p-STAT3/p65 and Bcl-2 activation.

Several in vivo studies on tumor xenograft mice model suggested the potential of piper longum or its active constituents in cancer therapeutics. Wang et al. [28] have reported that piperlongumine, a natural product isolated from the fruit of Piper longum, exhibits significant anti-tumor effects against human pancreatic carcinoma in an in vivo xenograft model and this compound enhanced the therapeutic effects of a chemotherapeutic drug, gemcitabine. There are various Indian traditional plants but to summarise, all these plants possess anti-tumor property which should be studied further in tumor xenograft models and clinical trials either alone or in combination with currently used chemotherapeutic drugs in order to identify an efficient, cost effective and less toxic treatment modality for the malignancy. In addition, quality of life of cancer patients could also be improved by the administration of medicinal plants. Therefore, collectively, Indian traditional medicinal plants could prove to be a proficient therapeutic approach as an adjuvant therapy to treat cancer in future.

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