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JMSR

REVIEW ARTICLE

Role of traditional medicines in the management of cancer

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Abstract

Context: Increasing numbers of cancer patients are looking towards traditional medicines (TM) in an effort to sustain tumour remission or halt the metastasis. TM such as Chinese Traditional Medicines, Ayurveda and Unani Medicines are being used in many parts of world from centuries. However, scientific data is lacking for the clinical use of majority of these medicines in cancer management and systematic clinical evaluation is mandatory before recommending long term use.

Objective: The role of traditional medicine for prevention and management of cancer are reviewed in this paper which will help to take a step further to bring these TM into mainstream therapy.

Methods: Traditional knowledge about the claims of therapeutic potential is collected. Emphasis was given to the use of plant derived products. Further efforts were made to identify the driving factors for use of such TM for the cure of cancer.

Results: There are several driving factors which attract patients towards TM out of which minimum side effects of TM remains on the priority. Apart from being used as standalone therapy, TM is progressively becoming more popular as adjuvant therapy to improve effectiveness of conventional treatment and to reduce the side effects of chemotherapy or radiation therapy.

Conclusion: Patients are inclining towards TM due to diverse reasons. The search for anticancer drugs from herbs has been very productive and advances in pharmacological techniques have exerted enormous drive on the research and development of new biologically active compounds of plant origin, which may act alone or in synergistic manner.

Keywords: Unani system; Ayurveda; Oncology; Herbal therapy; Complimentary therapy

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Received 08 July 2014; *Revised* 10 September 2014; *Accepted* 22 September 2014

Citation: Mohammed Husain G, Abdul Waheed M (2014) Role of traditional medicines in the management of cancer. J Med Sci Res 2(4):215-224. DOI: http://dx.doi.org/10.17727/JMSR.2014/2-038

Introduction

Despite strong understanding of the molecular basis and advances in treatment strategies, cancer remains the second major cause of death worldwide. Globally, there were 1,40,90,100 new cases of cancer in 2012. In India, there were about 10,14,900 new cases of cancer and about 6,82,800 people died from cancer in 2012. According to the latest World Cancer Report from the World Health Organisation, more women in India are being newly diagnosed with cancer annually. In India, 5,37,500 women were diagnosed with cancer compared to 4,77,500 men, during 2012. Most deaths in India (and in most low-income or middle-income countries) occur at home and without medical attention [1]. Among males and females, breast cancer alone is expected to cross the figure of 100,000 by the year 2020 [2].

Traditional medicines have been used for healing as well as preventative health for thousands of years all around the world. There are two different terms in relation to traditional medicines viz. complementary treatment and alternative treatment. Complimentary treatments are used in combination with mainstream therapy (conventional therapy) and are usually intended to treat side effects rather than to cure cancer tissue per se. On the other hand, alternative treatments are used in place of conventional therapy and are usually have their own therapeutic potential. With regard to cancer, there is widespread disappointment concerning conventional medicine and its inability to effectively cure several types of cancers. Further more, side effects of chemotherapy have become increasingly intolerable to the public focused on natural products and looking for more gentle and more effective substitutes for mainstream cancer treatments [3]. Traditional Chinese medicines have been applied for the treatment of cancers in China as well as many part of the world [4]. Approximately 50-60% cancer patients in the United States utilize agents derived from different parts of plants or nutrients (complementary and alternative medicine), either as standalone or concurrently with traditional therapeutic regime such as chemotherapy and/or radiation therapy [5]. The most popular alternative cancer therapies include restrictive diets, mind-body interventions, high-dose nutritional supplementation, and herbal therapy [3, 6]. Functional foods for prevention of chronic diseases are becoming quite popular now [7]. Other strategies of cancer prevention in human beings are increased consumption of functional foods like whole grains (brown rice, barley, and buckwheat) and by-products, as well as some fruits (berries, grapes, pineapple, citrus fruits), vegetables (bitter melon, garlic, ginger, onions, broccoli, and cabbage), and mushrooms. In addition, some beverages (green tea and coffee) may also act as protective against cancer [8, 9].

Herbs for the management of cancer

There are multiple mechanisms proposed for anticancer activity of herbs. The major mechanisms through which herbs are reported to act include antioxidant, apoptosis, cyclooxygenase-2 (COX) inhibition and angiogenesis inhibition. Most natural products target multiple gene products and thus are ideally suited for prevention and treatment of various chronic diseases including cancer which involve defects in multiple pathways [10]. The commonly used plants and plant derived products are reviewed in the following section of the article.

Aegle marmelos

Aegle marmelos (L.) Corr. Serr. commonly known as Bael and belongs to the family Rutaceae [11]. Bael is an important medicinal plant in the traditional Indian System of Medicine including Unani and Ayurveda [12]. Fruit, leaves and roots are reported to have medicinal values. Bael is growing in most of the Southeast Asia countries and reported to have various activities as antimicrobial activity, hypoglycemic, astringent, antidiarrheal, antidysenteric, demulcent, analgesic, anti-inflammatory, antipyretic, wound-healing, insecticidal, gastroprotective properties, radioprotective and antidiarrhoeal activity [13, 14]. *A. marmelos* extracts showed ability to inhibit the *in vitro* proliferation of human tumor cell lines, including the leukemic K562 [15, 16]. Hydroalcoholic extract of *A. marmelos* showed immunomodulatory effects and protection against N-methyl N-nitrosourea-induced hepatocarcinogensis in Balb/c mice [17]. Oral administration of *A. Marmelos* extract was found to be significantly effective in reducing skin tumors against chemical carcinogenesis in mice at the dose of 50 mg/kg body weight per day [18]. Recently, petroleum ether extract of *A. marmelos* also reported to elicit strong antitumor effects, while reducing murine ascites tumor volume and viable tumor counts and found equally effective as

cyclophosphamide and 5-fluorouracil especially when prophylactic administration was done [19]. The mechanism of anticancer activity may be due to antioxidant and immunomdulation effect. Hydroalcoholic extract of the fruit of *A. Marmelos* protects mice against gamma radiation induced toxic effects [20, 21].

Caraway

Carum carvi also known as meridian fennel or Persian cumin, is native to western Asia, Europe, and northern Africa. The principal agents in caraway oil are carvone or p-mentha-1,8-dien-2-one and limonene or p-mentha-1,8-diene, the precursors of carvone and anethofuran [22]. Caraway is reported to inhibit tumorigenesis and formation of aberrant crypt foci in rats [23] and supplementation of caraway at a dose of 60 mg/kg had a modulatory role on tissue lipid peroxidation and prevented 1,2-dimethylhydrazine(DMH)-inducedhistopathological lesions in colon cancer in rats [24]. Further, the inhibition of colon premalignant lesions induced by DMH is reported to be mediated by interference of caraway oil components in the activities of the main hepatic xenobiotic metabolizing enzymes [25]. Recent report indicates that the Wnt/β-catenin signaling pathway is activated during colon cancer promotion and that the expression of colonic β-catenin is altered in long-term caraway oil feeding, which lead to suppress DMH-induced premalignant lesions in rat colon [26].

Cardamom

Cardamom refers to herbs within the elettaria (green) and amomum (black) genera of the ginger family Zingiberaceae. It is a common ingredient used in cooking across India and various parts of Europe [15]. The potential of cardamom as a chemopreventive agent has been reported against two-stage skin cancer model in mice [27, 28]. Recently, *Elettaria cardamomumi* showed a significant immunosuppressive activity [29].

Clove

Clove is flower buds of the Eugenia caryophyllata, which contains several bioactive components including tannins, terpenoids, eugenol, and acetyleugenol (Kaefer and Milner, 2011). The essential oil extracted from the dried flower buds of clove, E. caryophyllata L. Merr. & Perry (Myrtaceae), is used as topical application to relieve pain and to promote healing and also used in the fragrance and flavouring industries [30]. Eugenol is a major component of essential of clove and it is reported that eugenol transduced the apoptotic signal via ROS generation, thereby inducing mitochondrial permeability transition, reducing anti-apoptotic protein bcl-2 level, inducing cytochrome c release to the cytosol, and subsequent apoptotic cell death [31]. Inducible COX-2 has been implicated in the pathways of inflammation and carcinogenesis. Thus, the potential COX-2 inhibitors have been considered as anti-inflammatory or cancer chemopreventive agents. Eugenol has been reported to inhibit the proliferation of HT-29 cells and the mRNA expression of COX-2, but not COX-1, which suggests that eugenol might be a plausible lead candidate for further developing the COX-2 inhibitor as an anti-inflammatory or cancer chemopreventive agent [32, 33]. Moreover, the oxidative damage of lipid, protein and DNA is known to be involved in chronic inflammation as well as metastasis and eugenol is reported to be beneficial for prevention of metastasis related to oxidative stress [34, 35].

Coriander

Coriander (*Coriandrum sativum* L.), a herbal plant, belonging to the family Apiaceae [36] and is native to southern Europe and northern Africa to south western Asia (Kaefer and Milner, 2011). All parts of this herb are in use as flavouring agent and/or as traditional remedies for the treatment of different disorders. Due to the presence of a multitude of bioactive constituents, a wide array of pharmacological activities have been ascribed to different parts of this herb, which include anti-microbial, anti-oxidant, anti-diabetic, anxiolytic, anti-epileptic, anti-depressant, anti-mutagenic, anti-inflammatory, anti-dyslipidemic, anti-hypertensive, neuro-protective and diuretic activity [36, 37]. The use of coriander oil as an added food ingredient is considered safe based on the history of consumption of coriander oil without reported adverse effects and lack of its toxicity in limited studies as well as lack of toxicity of its major constituent, linalool [38]. *Coriandrum sativum* seeds were found to be protective against DMH-induced colon cancer in rats [39]. Antioxidant and anticancer properties of *C. sativum* root extract are also reported which indicate that it could be useful as supplements in

combination with conventional drugs to enhance the efficacy of treatment of diseases such as cancer [40].

Turmeric

Turmeric, also known as golden spice is obtained from the rhizome of the plant *Curcuma longa* L. belonging to the family Zingiberaceae. It has been used to give colour and taste to food preparations since ancient times. Traditionally, turmeric has been used in India for the treatment of gynecological problems, gastric problems, hepatic disorders, infectious diseases, and dermatological problems [41, 42]. Various chemical constituents have been isolated from turmeric, including polyphenols, sesquiterpenes, diterpenes, triterpenoids, sterols, and alkaloids. Curcumin, which constitutes 2-5% of turmeric, is one of the most-studied plant constituent. Cell-based studies have demonstrated the potential of turmeric as an antimicrobial, insecticidal, larvicidal, antimutagenic, radioprotector, and anticancer agent. Numerous animal studies have shown the potential of turmeric against proinflammatory diseases, cancer, neurodegenerative diseases, depression, diabetes, obesity, and atherosclerosis. Curcumin is a highly pleiotropic molecule with a potential to modulate the biological activity of a number of signaling molecules. Curcumin can be used for chemoprevention of multiple cancers and modulates multiple molecular pathways involved in the complex carcinogenesis process to exert its chemopreventive effects through several mechanisms such as promoting apoptosis, inhibiting survival signals, scavenging reactive oxidative species, and reducing the inflammatory cancer microenvironment [43]. Curcumin is reported to inhibit COX-2 activity, cyclin D1 and MMPs over-expression, NF-kB, STAT and TNF-alpha signaling pathways and regulates the expression of p53 tumor suppressing gene [44]. By regulating multiple important cellular signalling pathways curcumin is known to activate cell death signals and induce apoptosis in pre-cancerous or cancer cells without affecting normal cells. Several phase I and phase II clinical trials indicate that curcumin is quite safe and may exhibit therapeutic efficacy [45]. Curcumin is well-tolerated but the only limiting factor is its low aqueous solubility which hampers its use as therapeutic agent [46]. Various formulations of curcumin are now available including nanoformulation with improved bioavailability [47].

Garlic

Garlic (*Allium sativum* L., Family: Liliaceae) is one of the oldest of all cultivated plants. It has been used as a medicinal agent for thousands of years. Garlic has multiple beneficial effects such as antimicrobial, antithrombotic, hypolipidemic, antiarthritic, hypoglycemic and antitumor activity. Studies have demonstrated the chemopreventive activity of garlic by using different garlic preparations including fresh garlic extract, aged garlic, garlic oil and a number of organosulfur compounds derived from garlic. The chemopreventive activity has been attributed to the presence of organosulfur compounds in garlic [48]. Several mechanisms are proposed for observed anti-tumor activity such as effect on drug metabolizing enzymes, antioxidant properties and tumor growth inhibition. Recently, it has been observed that aged garlic extract, but not the fresh garlic extract, exhibited radical scavenging activity. The two major compounds in aged garlic, S-allylcysteine and S-allylmercapto-L-cysteine, have the highest radical scavenging activity. Diallyl disulfide, a major organosulfur compound derived from garlic, can decrease carcinogen-induced tumors in experimental animals and inhibit the proliferation of various types of cancer cells [49]. It is reported mechanisms of action include: the activation of metabolizing enzymes that detoxify carcinogens; suppression of the formation of DNA adducts; antioxidant effects; regulation of cell-cycle arrest; induction of apoptosis and differentiation; histone modification; and inhibition of angiogenesis and invasion [49]. Studies have also shown that diallyl trisulfide, a garlic-derived bioactive compound, can offer protection against chemically-induced neoplasia as well as oncogene-driven spontaneous cancer development in experimental rodents [50]. Garlic is also reported to inhibit cell proliferation and induction of apoptosis, as well as suppression of COX-2 activity along with significant reduction in the incidence of aberrant crypt foci in azoxymethane induced colon carcinogenesis model in rats [15]. However, in spite of the abundance of pre-clinical reports on anti-tumor potential of garlic, clinical validation is lacking and a recent meta-analysis concluded that there is no evidence that higher intake of allium vegetables reduces risk for colorectal cancer [51].

Ginger

Ginger (*Zingiber officinale* Rosc.) belongs to

Zingiberaceae family and is consumed widely as a spice and condiment as well as medicinal agent (Kaefer and Milner, 2011). Ginger is traditionally used in various cultures for treating common colds, fever, to aid digestion, treat stomach upset, diarrhoea, nausea, rheumatic disorders, gastrointestinal complications and dizziness. Preclinical studies have also shown that ginger possesses chemopreventive and antineoplastic properties [52]. The anticancer potential of ginger is well documented and its active constituents like gingerols, shogaol, and paradols can prevent various cancers [53]. It is also reported to be effective in ameliorating the side effects of γ-radiation as well as chemotherapeutic agent doxorubicin and cisplatin. Ginger also inhibit the efflux of anticancer drugs by P-glycoprotein (P-gp) and reported to possess chemosensitizing effects in certain neoplastic cells *in vitro* and *in vivo* [54]. Crude ethanolic extract of ginger showed promising anticancer activity against cholangiocarcinoma without any significant toxicity, in the *in vitro* and *in vivo* studies [55]. A natural compound isolated from the rhizome of ginger (i.e., 6-Shogaol) is reported to induce apoptosis and G2/M phase arrest in human cervical cancer HeLa cells [56]. 6-Shogaol is reported to be more effective than two other compounds found in ginger, 6-gingerol and 6-paradol at reducing survival of prostate cancer cells and reducing STAT3 and NF-κB signalling. 6-Shogaol also showed significant tumor growth inhibitory activity in an allograft model using HMVP2 cells [57]. Ginger extract, has limited therapeutic utilization due to poor bioavailability and physicochemical properties. Ginger extract loaded alginate beads were reported to improve its biopharmaceutical performance in the distal parts of gastrointestinal tract for the treatment of colon cancer in rats [58].

Rosemary

Rosemary (*Rosmarinus officinalis* L.) is a common household plant grown in many parts of the world. It is used for flavouring food, beverages and also used in cosmetics. In traditional medicine, it is used as an antispasmodic in renal colic and dysmenorrhoea, in relieving respiratory disorders and to stimulate growth of hair [59]. Extract of rosemary relaxes smooth muscles of trachea and intestine, and has choleretic, hepatoprotective and antitumerogenic activity. The most important constituents of rosemary are caffeic acid and its derivatives such as rosmarinic acid. *R. officinalis* essential oil showed greater activity than its isolated constituents in both antibacterial and anticancer test systems [60]. Carnosic acid, the main antioxidant compound of *R. officinalis* is reported to inhibit the cell viability of three colorectal cancer cell lines [61]. Literature evidence from animal and cell culture studies demonstrates the anticancer potential of rosemary extract, carnosol, carnosic acid, ursolic acid, and rosmarinic acid [62]. Nabekura et al. 2010, suggested that rosemary constituents, such as carnosic acid, have inhibitory effects on anticancer drug efflux transporter P-glycoprotein and may become useful to enhance the efficacy of cancer chemotherapy [63]. Extract of *R. officinalis* reported to have a protective effect on plasmid DNA damage, and at concentrations of 10-80 microg/mL was able to reduce significantly the growth of M14 and A375 melanoma cell lines [64]. Anti-angiogenic activity of carnosol and carnosic acid could contribute to the chemopreventive, antitumoral and antimetastatic activities of rosemary extracts and suggests their potential in the treatment of other angiogenesis-related malignancies [65]. Extract of *R. officinalis* is reported to have radioprotection potential. Treatment of mice with extract of *R. officinalis* delayed the onset of mortality and reduced the symptoms of radiation sickness when compared with the non-drug-treated irradiated controls [66, 67].

Saffron

Saffron obtained from the dried stigmas of *Crocus sativus* L., is an important spice, rich in carotenoids, consumed in different parts of the world. Saffron possesses free radical-scavenging properties and antitumor activities. Significant cancer chemopreventive effects have been shown in both *in vitro* and *in vivo* models [68]. Anticancer activity of saffron extract (dimethyl-crocetin) or its derivatives is reported against a wide spectrum of murine tumors and human cell lines [69-74]. The genotoxic potential of anti-tumor drugs limits their efficacy in the treatment of cancers. Pre-treatment with saffron significantly inhibited anti-tumor drugs induced cellular DNA damage (strand breaks) as revealed by decreased comet tail length, tail moment and percent DNA in the tail, which suggest a potential role for saffron as an anti-genotoxic, anti-oxidant and chemopreventive agent and could be used as an adjuvant in chemotherapeutic applications [75].

Crocetin, an important carotenoid constituent of saffron, has shown significant potential as an anti-tumor agent in animal models and cell culture. Crocetin affects the growth of cancer cells by inhibiting nucleic acid synthesis, enhancing anti-oxidative system, inducing apoptosis and hindering growth factor signalling pathways [5]. Saffron is reported to exert significant chemopreventive effect against liver cancer through inhibition of cell proliferation and induction of apoptosis [76]. Saffron extract also exhibited anticancer effect in two p53 isogenic colorectal cancer cell lines [77]. Aqueous extract of saffron also reported to inhibit the chemically-induced gastric cancer progression in the rats [78].

Several hypotheses for the antitumor actions of saffron and its constituents have been proposed such as inhibitory effect on cellular DNA and RNA synthesis, but not on protein synthesis; the inhibitory effect on free radical chain reactions; the metabolic conversion of naturally occurring carotenoids to retinoids; and the interaction of carotenoids with topoisomerase II, an enzyme involved in cellular DNA-protein interaction. Bolhassani A et al. [79] and Samarghandian S et al. [80] have nicely reviewed these biochemical activities and anti-tumor mechanism of saffron.

Role of traditional medicines as adjuvant therapy in cancer

The toxic adverse effects of anticancer therapy are major limitations to their effective use and also affect the quality of life. It has been observed that some traditional medicines are very effective in reducing the toxic effects of chemotherapy/radiation therapy. In such conditions, although traditional medicines do not exhibit anti-tumor effect per se, but improve the tolerability (as well as effectiveness) of conventional anti-cancer therapies. Several hypotheses are proposed regarding their beneficial effect as adjuvant therapy. Immunomodulation plays a critical role in the efficacy of herbal medicines for cancer. Many cancer patients with advanced malignancy do have lowered levels of innate immunity. A variety of herbal medicines and plant compounds directly stimulate this innate immune response as well as protect bone marrow against the myelosuppressive effects of conventional chemotherapy [9]. An important category of such plant is 'Adaptogens', which are nonspecific, nontoxic, and normalizing agents [9]. The effect produced by adaptogens varies according to the physiopathological state. For example, Ginseng is an angiogenic in wound healing, while it is antiangiogenic in cancer. Adaptogens like Ginseng and Ashwagandha (also known as Asgand in Unani medicine) have multiple anticancer effects, as well as beneficial interactions with conventional chemotherapy and radiation [9].

Hypericum japonicum Thunb. extract is reported to enhance the efficacy of 5-fluorouracil treatment in murine liver tumor xenografts and reduction of toxicity of chemotherapy in hepatoma H22-bearing mice [81]. Diarrhoea and nausea are common side effects of irinotecan, and ulceration and intestinal bleeding can occur following its administration as the drug causes cell death and inflammation in the intestine [82]. PHY906 (a mixture of four herbs), which is derived from an ancient Chinese medicine used to treat nausea, vomiting and diarrhoea, has been shown to reduce diarrhoea and nausea in initial trials in patients receiving irinotecan. Although PHY906 does not provide protection from chemotherapy induced gastrointestinal damage, it does stimulate the recovery of intestinal cells by promoting progenitor cell repopulation and inhibiting inflammatory responses [83]. In a double-blind placebo-controlled randomized study of Chinese herbal medicine, although no reduction of the hematologic toxicity was observed, however, a significant control of nausea is reported [84]. Many published studies reflect the growing application of complementary and alternative medicine, particularly Chinese herbal medicine use in combination with conventional cancer therapy for advanced non-small cell lung cancer. Anticancer herbs used in Chinese medicine are classified into four groups viz. eliminating pathogenic factors, strengthening the body resistance, enhancing effects of chemotherapy and detoxication of chemotherapy [85]. A systematic review suggests that Chinese herbal medicine as an adjuvant therapy can reduce chemotherapy toxicity, prolong survival rate, enhance immediate tumor response, and improve Karnofsky performance score in advanced non-small cell lung cancer patients. However, due to the lack of large-scale randomized clinical trials, further larger scale trials are needed [86].

Herb-chemotherapeutic drugs interaction

Some herbs may lead to interaction with

conventional anti-cancer agents and may cause lack of effectiveness or may even increase side effects when used concurrently. For example, St John's wort (*Hypericum perforatum*) can reduce the effectiveness of the chemotherapy drug irinotecan and imatinib [87, 88]. It can also cause photosensitivity and could increase skin reactions to radiotherapy. Similarly green tea may increase the side effects caused by the chemotherapy drug irinotecan and tamoxifen [89]. Herbal medicine such as garlic, ginkgo, echinacea, ginseng, St John's wort, and kava have been reported to significantly modulate the activity of drug-metabolizing enzymes such as cytochrome P450 and/or the drug transporter P-glycoprotein. Such herbs participate in potential pharmacokinetic interactions with anticancer drugs when administered concurrently [90]. Moreover, considering the narrow therapeutic window of anticancer drugs, the use of traditional medicines increases the risk of clinically relevant herbs-anticancer drug interactions [91]. Evidence-based studies should be undertaken to document the positive and/or negative effects of the concomitant use of herbs with anticancer chemotherapeutic drugs [92].

Conclusion

Multi-disciplinary studies published in recent years have demonstrated that traditional medicines have a lot to offer for the management of cancer. The only priority is to scientifically evaluate these valuable therapeutic options and generate evidence based data for global acceptance of these traditional medicines. Another thrust area must be the safety of these traditional medicines and their interaction potential with existing mainstream chemotherapy or radiation therapy. The interaction with chemotherapy is more critical in case of adjuvant therapy because there are several reports clearly indicating interaction potential of few herbs with chemotherapeutic agents. In such a scenario, specific studies are warranted to optimize the dose requirement and to demonstrate the pharmacokinetic profile when they are concurrently used in patients. Additionally much emphasis is required on the preventive anticancer aspects of traditional medicines. Overall, integrative treatment strategies must be developed and adopted by mutual coordination of healthcare professionals working under different domains for the betterment of mankind.

Acknowledgments

The library services of the CCRUM-Central Research Institute of Unani Medicine, Hyderabad are gratefully acknowledged.

Conflict of interest

The authors declare that they have no conflict of interest.

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