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Ayurveda as an Adjuvant Medication for Combating Cancer: A Review

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Abstract

Cancer is one of the most dreaded diseases of the 20th century and spreading further with continuance and increasing incidence in 21st century. At present Chemoprevention and Radiotherapy is main stay of management. But these can produce toxic side effects, which have limited their extensive use. Ayurveda drugs available in different part of the world have been extensively studied for their anti-cancer activity. Ayurveda also have provided with many such drugs which can be proved to be a good anti-cancer substitute to conventional treatment or also provide benefit as an adjuvant therapy. Researches on many such Ayurvedic plants available in India like *Azadirachta indica*, *Carica papaya*, *Plumbago zeylanica*, *Ocimum sanctum*, *Tinospora cordifolia, Catharanthus roseus* are reviewed, and found to be effective as anti-cancer in many types of cancers and adjuvant therapy along with chemotherapy and radiotherapy. There is a broad scope to derive the potent anticancer agents from medicinal plants, which need thorough research. Present review reveals the anticancer potential of various Ayurveda drugs so that the findings can be applied in the benefit of cancer patient.

Keywords: Ayurveda; Cancer; Adjuvant anti-cancer

Abbreviations: SCC: Squamous Cell Carcinoma; HCC: Hepatic Cell Carcinoma; NSCLC: Non-Small Cell lung cancer

Introduction

Cancer is one of the most dreaded diseases of the 20th century and spreading further with continuance and increasing incidence in 21st century. Cancer is a major cause of morbidity and mortality in developing and developed countries alike [1]. In many low-income and middle-income countries, including India, most of the population does not have access to a well-organized and well regulated cancer care system. As per a study the total cancer cases in India are likely to go up from 979,786 cases in the year 2010 to 1,148,757 cases in the year 2020 [2].

Chemoprevention is a rapidly growing area of oncology which focuses towards the cancer preventive strategy of natural or synthetic interventions. Chemoprevention also deals with the chemotherapy of pre-cancer lesions, which are called pre-invasive neoplasia, dysplasia or intra-epithelial neoplasia depending on the organ system. Chemoprevention by synthetic agents can produce toxic side effects, which have limited their extensive use.

As cancer cells grow and divide more rapidly than normal cells, anticancer drugs being used at present are cytotoxic in nature intended for targeting rapidly multiplying cells and the putative targets are the nucleic acids and their precursors, which are rapidly synthesized during cell division. But certain normal, healthy cells also multiply quickly, and chemotherapy can affect these cells, too. This damage to normal cells causes side effects. The fast-growing, normal cells most likely to be affected are blood cells forming in the bone marrow and cells in the digestive tract (mouth, stomach, intestines, esophagus), reproductive system (sexual organs), and hair follicles. Some anticancer drugs may affect cells of vital organs, such as the heart, kidney, bladder, lungs, and nervous system. The side effects may be acute or chronic, self-limited, permanent, mild or potentially life threatening [3]. Management of these side effects is of utmost importance because they affect the treatment, tolerability and overall quality of life, in this aspect Ayurveda can be proved as an important adjuvant to curb these side effects.

Medicinal plant derived drug research has made significant progress in anticancer therapies. Nature has bestowed our country with an enormous number of medicinal plants therefore India has often referred to as the medicinal garden of the world. In the armory of modern medicine, the components of synthetic drugs or the medicinally accepted plants are evaluated for their efficacy against certain diseases thus forming a valuable source of therapeutic agents. Plants used against cancer lists more than 3000 species that have reportedly been used in the treatment of cancer [4]. The focus was on the main Ayurvedic drugs, but it is interesting to note that no new plant-derived clinical anti-cancer agents have, as yet, reached the stage of general use. However a number of agents are under preclinical development. Given below are some of such Ayurvedic drugs which are yielding successful results in the drug development against cancer.

Aim of Study

This review aims at scanning the scattered literature on the anti-cancer properties of Ayurvedic drugs and provides their scientific evidences.

Method

Classical texts of Ayurveda as well as PubMed, MEDLINE database were used for the search of relevant literature and research papers. Papers published between Jan 1960 to Jan 2015 were only considered. The key words used for the search was 'Ayurveda', 'Anti-cancer' etc. *In-vitro* analysis, experimental trials as well as clinical studies were included in the review to search out the reported therapeutic potential of Ayurvedic drugs. Only research articles published in English language were considered.

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List of Few Ayurveda Drug Helpful in Management of Cancer

Azadirachta indica [5]

(Neem tree) has been used successfully to reduce tumors in Ayurveda from centuries. Recent studies indicated that an ethanolic extract of neem has been shown to cause cell death of prostate cancer cells (PC-3) by inducing apoptosis as evidenced by a dose-dependent increase in DNA fragmentation and a decrease in cell viability [6]. Different studies indicate its use against buccal carcinogenesis, skin carcinogenesis, prostate cancer, Ehrlich carcinoma and B16 melanoma [7]. Neem extracts have been shown to possess potent anti-cancer properties against oral squamous cell carcinoma, [8,9] and induces apoptosis in 4T1 breast cancer BALB/c Mice [10]. Nimbolide, a limonoid present in leaves and flowers of the neem tree, have apoptosis-inducing property [11,12] thus beneficial in human breast cancer [13].

Studies have shown that *A. indica* has got a chemo preventive capability by regression of the DEN/AAF (diethyl nitrosamine/2-acetylaminofluorene) induced carcinogenesis in liver [14,15]. These results indicate that dietary use of extracts from various parts of *A. indica* may play a promising role in future drug discovery and development programs as far as chemoprevention of cancer is concerned.

As adjuvant therapy: Lower dose combinations of ethanolic neem leaves extract with cisplatin resulted in synergistic growth inhibition of these human breast (MCF-7) and cervical (HeLa) cancer cells, thus help in potentiating the ability of anti-cancer drug in the effective management of cancer [16].

Carica papaya (Papita)

It is an extensively used fruit in India. A recent study [17] found that papaya leaf extract could prevent growth of cancer cells, including pancreatic cancer - one of the most devastating forms of cancer [18]. Papaya leaf not only contained phenolic compounds but it also had a substantial content of saponins, which was significantly higher than the level of phenolic compounds [19]. Saponins, which have been associated with the prevention of cancer, are structurally amphiphilic, containing hydrophilic (carbohydrate) and hydrophobic (steroid or triterpene) moieties [20].

As an adjuvant therapy: In patients with locally advanced cancer of the uterine cervix, oral enzyme therapy (with papain) was found to be effective in significantly reducing radiation therapy-related side effects such as genitourinary symptoms, subcutaneous changes and reactions of the vaginal mucosa [21]. In another study complementary treatment of colorectal cancer patients with papain as oral enzyme medication improves their quality of life by reducing both the signs and symptoms of the disease and the adverse reactions associated with adjuvant antineoplastic therapies [22].

Plumbago zeylanica (Chitraka)

Active constituent of Plumbago, Plumbagin was reported to act against P388 lymphocytic leukemia [23]. A study, have found that plumbagin effectively inhibited three kinds of NSCLC (non-small cell lung cancer) cell lines including A549, H262, and H460 growth *in vitro*, concomitant with induction of apoptosis [24]. Reports have shown that plumbagin induced apoptosis through the mitochondrial-mediated pathway in breast cancer and lung cancer [25-27]. Plumbagin also exhibits anticancer activity by inactivation of oncogenic transcription factor Forkhead Box M1 (FOXM1) signaling pathway in glioma cells. [28] Plumbagin modulates cellular proliferation, carcinogenesis, and radioresistance, all known to be regulated by the activation of the transcription factor NF-κB, suggesting plumbagin might affect the NF-κB activation pathway [29]. Plumbagin induce apoptosis in human pancreatic cancer cells primarily through the mitochondria-related pathway followed by both caspase-dependent and caspase-independent cascades. It indicates that plumbagin can be potentially developed as a novel therapeutic agent against pancreatic cancer also [30].

Ocimum sanctum (Tulsi)

Ocimum sanctum contains eugenol, linolenic acid, rosmarinic acid and flavonoids such as orientin, vicenin, cirsilineol, cirsimaritin, isothymusin, isothymonin and apigenein. Eugenol, orientin and vicenin inhibits growth and spread of various cancers such as breast cancer, liver cancer and sarcomas particularly fibrosarcoma by blocking supply of oxygen and nutrients to the cancer cells and killing them by starving [31]. Anticancer and chemopreventive properties of Ocimum have been reported [32]. Topical application of Ocimum extract significantly reduced the cumulative number of papillomas in 7,12-dimethylbenz(a)anthracene-induced skin papillomagenesis in rats [33]. A significant 2-fold elevation of reduced glutathione content and increased glutathione S-transferase activity was also observed in the skin of extract treated animals. Rat hepatocytes pretreated with the extract and then with dimethylbenz anthracene (DMBA) showed significant reduction in DMBA-DNA adducts [34]. Studies reported that administration of *O. sanctum* to mice significantly elevated glutathione and more than 78% of glutathione S-transferase activity and prevented forestomach tumors and hepatomas. Hence, an increase in survival rate [35,36], Ocimum ethanolic extract investigated against human fibrosarcoma cells (HFS cells) in culture. The DNA was found to be fragmented on observation in agarose gel electrophoresis. Biochemically the extract-treated HFS cells showed depleted intracellular glutathione and increased levels of lipid peroxidation products [37].

As an adjuvant: Beneficial effects of the extract of this plant have also been reported in radiotherapy of human cancer [38].

Tinospora cordifolia (Guduci)

Administration of polysaccharide fraction from *Tinospora cordifolia* was found to be very effective in reducing the metastatic potential of B16F-10 melanoma cells [39]. Studies have shown that *Tinospora cordifolia* prevents the micronucleus formation in dose dependent manner and in melanoma tumor model, *T. cordifolia* have a preventive effect on tumor volume, with increment in mean survival time [40]. Intraperitoneal injection of the alcoholic extract of *T. cordifolia* to Dalton's lymphoma (DL) bearing mice have stimulated macrophage functions like phagocytosis, antigen presenting ability and secretion of interleukin-1 (IL-1), tumour necrosis factor (TNF) and reference nutrient intake (RNI) as well as slowed tumor growth and increased lifespan of the tumor-bearing host [41]. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a tumor-bearing host [42]. Palmatine found in *Tinospora cordifolia* is a close structural analog of berberine that has been shown to exhibit significant antitumor activity against HL-60 leukemic cells [43]. Palmatine enhance the antioxidant enzyme levels for antioxidant enzyme activity like GSH, SOD, catalase, and inhibited lipid peroxidation hence showing its role in detoxification pathway. Both enzyme activities and histological analysis suggest that environmental carcinogens that induce skin carcinogenesis can be inhibited by oral administration of palmatine in the daily diet to achieve protection against skin cancer and can inhibit papilloma growth [44] (Table 1).

S.No.	Ayurvedic drug	List of anticancer alkaloid	Type of cancer effective against
1	*Azadirachta indica*	Nimbolide, limonoid	Prostate cancer cells, buccal (S.C.C.) and skin cancer, Ehrlich carcinoma and melanoma, H.C.C., breast cancer
2	*Carica papaya*	Saponins, triterpene, papain	Pancreatic cancer, cancer of uterine cervix, colorectal carcinoma
3	*Plumbago zeylanica*	Plumbagin	Lymphocytic leukemia, N.S.C. lung cancer, breast carcinoma, pancreatic cancer
4	*Ocimum sanctum*	Eugenol, linolenic acid, rosmarinic acid, orientin and vicenin	Papillomas, breast cancer, liver cancer and fibrosarcoma
5	*Tinospora cordifolia*	Palmatine	Melanoma cells, Dalton's lymphoma, leukemia, skin cancer, neck cancer
6	*Catharanthus roseus*	Vincristine and Vinblastine	Leukemias, lymphomas, solid tumors, large-cell non-Hodgkin's lymphomas, Wilms tumor, neuroblastoma, rhabdomyosarcoma, bladder cancer, testicular carcinomas

Table 1: List of anticancer ayurveda drugs, anticancer alkaloids and the efficacy against cancer type.

As an adjuvant therapy: *Tinospora* is effective for prevention of mucositis in patients with head and neck cancer receiving Radiotherapy [45]. *Tinospora cordifolia* showed radioprotective effects in mice exposed to lethal doses of radiation [46]. It induced enzymes of antioxidant system and in that way inhibited lipid peroxidation in mice. Lipid peroxidation by free radicals is one of the mechanisms by which radiotherapy produces its severe side effects [47]. If *Tinospora cordifolia* can prevent this from happening and if it exhibits the same mechanism of action in humans, these findings would be an amazing support for patients undergoing radiotherapy.

Catharanthus roseus (Sadapushapi)

Methanolic extracts of Catharanthus was found to have significant anticancer activity against numerous cell types in the *in-vitro* condition [48] and especially against the multidrug resistant tumor types [49]. Nearly about twenty alkaloids of *Catharanthus* have oncolytic activity present in all the parts of plant like especially Vincristine and Vinblastine are among major alkaloid possessing oncolytic activity [50,51], and major part of these two alkaloid are present in leaves [52]. Vincristine present in *Catharanthus* is a standard component of regimens for treating pediatric leukemias, lymphomas, solid tumors, large-cell non-Hodgkin's lymphomas, and also is a standard component of regimens used to treat pediatric solid tumors such as Wilms tumor, neuroblastoma, and rhabdomyosarcoma and Vinblastine is more effective in bladder cancer, testicular carcinomas, and Hodgkin's disease. In a study *C. roseus* crude aqueous extract showed differential effects of inhibiting the proliferation of the Jurkat leukemic T cell line and promoting the growth of normal peripheral blood mononuclear cells (PBMCs). These data suggest that the extract may be applicable for modulating the normal and transformed immune cells in leukemia patients.

Conclusion

This paper was aimed at reviewing the anti-cancer activity of various Ayurveda plants and their role as an adjuvant therapy in cancer management. The review reveals that the plants *Azadirachta indica*, *Carica papaya*, *Plumbago zeylanica*, *Ocimum sanctum*, *Tinospora cordifolia* and *Catharanthus roseus* possess potent anti-cancer activity and therefore can be successfully used in cancer management both as mainline treatment or as an adjuvant medication with minimal adverse effects of its own or that of chemotherapy or radiotherapy. With the help of this paper the drugs which are quoted will prove to be beneficial for the researcher planning clinical trial with them and they can be used in the clinical practices for treating the cancers in near future. The selective and careful use of Ayurvedic plants will definitely prove to be beneficial in cancer management.

Declaration

This is to declare that none of the author has any competing interest in the manuscript.

Contributions

All the authors were involved in screening and collection of data and study.

Conflict of Interest

There is no conflict of interest.

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