Evidence-based review on anticancer effects of commonly used herbs

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Abstract

Cancer, a disease with high morbidity and mortality rates, is a challenge to human life. The current therapeutic strategies are associated with adverse effects which necessitate alternate treatment with less adverse effects. In addition to this, cancer prevention is desirable which has led to a new concept called biochemoprevention. In this regard, medicinal properties of plants can be exploited for cancer prevention and management as they can be procured cost effectively and are less likely to produce adverse effects as they are diet derived. This article reviews the phytochemicals and evidence-based preventive and therapeutic effects of some commonly used plants with medicinal properties against cancer.

Keywords

Biochemoprevention, cancer, medicinal properties of plants, phytochemicals

Introduction

Cancer continues to be a challenge to human life as the disease has high morbidity and mortality rates. Though surgery, chemotherapy, and radiotherapy remain the “Gold Standard” measures of cancer therapy, they are associated with adverse effects. Despite the recent advances in therapeutic strategies, the 5 years survival rate of one of the most commonly occurring cancer like oral cancer is as low as 62% with no improvement in the quality of life of the affected individuals. Hence, treatment modality with less adverse effects will be of great benefit to the affected patients. Furthermore, research in the field of oncology has led to better understanding of the molecular mechanisms of carcinogenesis that has revealed that cancer is a largely preventable disease. Hence, a new concept called biochemoprevention has evolved not only to prevent but also combat the shortcomings of cancer therapy. Chemoprevention or biochemoprevention refers to pharmacological intervention with synthetic or natural compounds that may prevent, inhibit, or reverse carcinogenesis.

The use of medicinal plants for the management of various diseases including cancer has been carried out several 100 years ago during the period of Charaka, the Father of Medicine and Susrutha, the Father of Surgery. With the advent of Modern medicine, traditional medicine has lost its importance. Hence, the medicinal properties of plants which are our natural resources must be re-explored to prevent and treat cancer. The advantages of utilizing medicinal properties of plants for cancer prevention and management include easy availability, cost effective, and less likely to produce side effects as most of these plants or plant parts are diet derived. This article highlights evidence-based preventive and therapeutic effects of some commonly used plants with medicinal properties against cancer.

Review

Neem

Azadirachta indica commonly known as neem in English and Vembu in Tamil is native to our country and is known for several medicinal properties including antimicrobial, antioxidant, anti diabetic. It also finds its use in preparation of cosmetics, toothbrush fertilizer, and toothbrush. This could be attributed to more than 140 compounds present in various parts of the plant. Recently, research has been carried out to demonstrate the antineoplastic effects of this plant. Ethanolic extract of neem leaves caused both
reduction in tumor size and decrease in tumor progression even after cessation of treatment with neem extract in N methyl N nitrosurea induced mammary tumors in Sprague Drawley rats. Molecular analysis revealed up-regulation of proapoptotic genes and proteins such as p53, B-cell lymphoma 2 (Bcl2), bax, caspases, phosphatase and tensin homolog, c-Jun N-terminal kinases and down-regulation of oncogenes such as vascular endothelial growth factor (VEGF), cyclin dependent kinase 1, nuclear factor kappa B (NF kappa B), mitogen-activated protein kinase 1 (MAP1). Glycoproteins present in neem leaves also exert anti-cancer effects by restricting tumor growth in murine, These proteins alter tumor microenvironment by increasing CD 8 (Cluster of differentiation 8) T-cells, protect T-cells from Anergy, decrease activation-induced T-cell death by decreasing expression of FAS receptor. Cytotoxicity of sarcoma cells was caused due to increased expression of perforin, granzyme B in lymphocytes. These results shed light on the fact that neem extracts possess immunomodulatory effects hence aid in targeted therapy against malignant cells, sparing normal cells. Hence, these extracts are less likely to produce side effects.

**Tulasi**

*Ocimum sanctum* commonly known as Tulasi in Tamil and Holy basil in English is a sacred plant of Hinduism. The aromatic plant has several medicinal properties and has been used several 1000 years ago for the management of various diseases and ailments like common cold, fever, acne, headache, stress, aphthous ulcers, asthma, bronchitis, tuberculosis, ecema. It also has been used as an expectorant for management of cough, antimicrobial agent in preventing diarrhea, analgesic for pain management. Other medicinal properties include immunomodulation, hypolipidemic, and hepatoprotective. Phytochemical constituents that confer these properties are oleic acid, uroseolic acid, rosmarinic acid, eugenol, carvacol, linalool, beta carophyllene, beta elemene, germaserene. *O. sanctum* possesses cancer preventive and therapeutic properties. Important phytochemicals such as eugenol, rosmarinic acid, apigenin, silosterol, carnosic acid, lutrolen, myrtenal present in tulasi prevent chemical-induced cancers of the skin, lung, oral cavity, liver by induction of apoptosis, prevention of angiogenesis and metastasis, antioxidant activity, and alteration of genes. Flavonoids such as ornitine, vicenin, protect normal tissue from therapeutic radiation and prevent radiation-induced mortality in mice. Eugenol, rosmarinic acid, and apigenin present in Holy basil prevent radiation-induced deoxyribonucleic acid (DNA) damage thereby acting as a chemopreventive agent.

Tulasi exerts radioprotective effects in oral cancer by causing a significant reduction of glutathione in erythrocytes of oral cancer patients who were treated with radiotherapy and flavonoids of *O. sanctum* in comparison with oral cancer patients who received only radiotherapy.

**Allium vegetables**

Allium vegetables like onion are used as flavoring and seasoning agent for food in many countries. Interestingly, two species of onion viz red onion (*Allium cepa*) and yellow onion (*Allium flavum*) possess medicinal properties.

Bulb of *A. cepa* contains flavonoids such as anthrocyanins and dihydroflavonols. The sulfur containing the active constituent of onion bulb occur mainly in the form of S-alkyl cysteine sulfoxides which decompose into thiosulfimates and polysulfides. Thiosulfimates are volatile sulfur compounds responsible for the pungent odor and medicinal properties. Onion exerts chemopreventive activity. The ethyl acetate extract of onion has been shown to induce apoptosis in human breast cancer cell lines. It also inhibits fatty acid synthase and lipid accumulation in adipocytes, thereby preventing obesity, one of the predisposing factors for breast cancer.

Yellow onion (*A. flavum*) also has anticancer activity. *A. flavum* extract has significant phenolic content, antioxidant, antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, and antiproliferative activity against homo sapiens colorectal carcinoma cell lines.

**Pineapple**

*Annamas cosmous* or pineapple is a tropical plant of Bromidiaceae family. Edible portion of this plant is the fruit which is made of coalesced berries. Pineapple has been used in South America, China, South East Asia for the management of various ailments like inflammation, burns as it exerts medicinal properties such as anti-inflammatory, anti-thrombotic, fibrinolytic, inhibition of platelet aggregation, and skin debridement. In 1957, Bromelain was identified as the active principle present in the stem and unripe fruits of pineapple exerting the above-mentioned activities. Bromelain is a mixture of proteases. Bromelain alters molecular pathways of carcinogenesis, tumor microenvironment hence could be used as an anticancer agent. Bromelain also exerts anticancer effects by immunomodulation and hemostatic mechanism.

Pineapple extract in stage 2 mouse skin tumorigenesis model cause reduction in tumor size (65%) and volume. Molecular analysis revealed up-regulation of p53, bax, caspase 3, 9 and down-regulation of Bcl2, inhibition of cyclooxygenase 2, inactivation of NF kappa B, MAP, extracellular-signal-regulated kinases, and protein kinase B.

**Cruciferous vegetables**

*Brassica oleracea* belongs to the family Brassiaceae, which are commonly known as cruciferous vegetables. In uncultivated form, it is called as wild cabbage and is native to Europe. Cabbage (*B. oleracea capitata*), Cauliflower (*B. oleracea botrytis*), Brocoli (*Brassica oleraceaitalica*) are some of the varieties of wild cabbage developed by various cultivars. These cruciferous vegetables are a part of the diet in many countries including India. Recently, research has been carried out to assess the phytochemical
constituents and medicinal properties of these vegetables. The leaves of cabbage contain two pyrrolidine which has been isolated and identified by gas chromatography, mass spectrometry, and high-performance liquid chromatography. This active constituent induces apoptosis and cell cycle arrest in GO/G1 phase in cervical cancer cell line taken from Henrietta Lacks (HeLa) and body cavity-based lymphoma cell line (BC-3 cell lines), hence possesses antimutant activity. B. oleracea also contains glucosinolates which on hydrolysis yields isothiocyanates that exerts antineoplastic effects. Sulforaphane is one such isothiocyanate that causes down-regulation of Bcl2 and up-regulation of p53, bax, caspase 3 in HeLa derivative (Hep 2 cell lines). Isothiocyanates have chemopreventive effects. These isothiocyanates modulate carcinogen metabolizing enzymes, thereby limited formation of reactive intermediates that from DNA adducts. Both intact glucosinolates and isothiocyanates modulate Phase II detoxification enzymes such as Quinone reductases, Glutathione-S-transferases, Epoxide hydrolase, Uridine 5'-diphospho-glucuronosyltransferase. Intact glucosinolates modulate cytochrome P450 enzymes line ethoxyresorufin-O-deethylase, ethoxyresorufin O-deethylase. Isothiocyanates and glucosinolates such as Phenyl isothiocyanates, erucin, sulforaphane are antagonists of aryl hydrocarbon receptor hence aid in cancer prevention.

**Apple**

Apple, the pomaceous fruit of *Malus domestica* tree belongs to the family Rosaceae. *Malus sieversi*, ancestor of this species is native to the mountains of Central Asia. It is one of the oldest known fruits that prevents lung cancer, chronic obstructive pulmonary disease, cardiovascular disease, thrombosis, and stroke. Polyphenols and flavonoids, the phytochemical constituents of apple fruit have antioxidant properties. The phytochemical components of apple can act as a chemopreventive agent due to the antioxidant and the antiproliferative property. Triterpenoids of apple peel possess antitumor activity. 2R-hydroxy-3α-([(2E)-3-phenyl-1-oxo-2-propenyl]oxy)olean-12-en-28-oic acid, 2R-hydroxysursolic acid, and 3α-trans-p-coumaroyloxy-2R-hydroxylauric-12-en-28-oic acid, the triterpenoids isolated from apple peel exerts higher antitumor activity against HepG2 cell lines. Ursolic acid, 3α-trans-p-coumaroyloxy-2R-hydroxylauric-12-en-28-oic acid, and 2R-hydroxysursolic acid are the terpenoids that have higher antineoplastic activity against Michigan Cancer Foundation-7 (MCF-7) cancer cells. Terpenoids such as 2R-hydroxy-3α-[([(2E)-3-phenyl-1-oxo-2-propenyl]oxy)olean-12-en-28-oic acid, 2R-hydroxysursolic acid, maslinic acid, and 3α-trans-p-coumaroyloxy-2R-hydroxylauric-12-en-28-oic acid have higher anticancer effects against heterogeneous human epithelial colorectal adenocarcinoma cells cancer cells. Apple peel extracts exert anticancer effects by causing Go/G1 cell cycle arrest, decreasing expression of proliferating cell nuclear antigen (PCNA), increasing the levels of the tumor suppressor protein maps in human prostate and breast carcinoma cells.

**Papaya**

*Carcia papaya* commonly known as papaya of the family Caricaceae, is cultivated throughout India. Leaves of papaya have been used to treat diseases and ailments such as jaundice, asthma, colic, fever, beriberi. Recent studies have demonstrated that papaya leaf extracts could be used for cancer management. Significant growth inhibitory activity of *C. papaya* leaf extract on a couple of cell lines including Raji and Ramos (Burkitt’s lymphoma cell lines), Jurkat (T cell Lymphoma cell line), HepG2 and Huh-7 (hepatocellular carcinoma cell lines), K562 (chronic myelogenous leukemia cell line) PC14 (lung adenocarcinoma cell line), HeLa (cervical carcinoma cell line, Panc-1 (pancreatic epitheliod carcinoma cell line), Capan1 (pancreatic adenocarcinoma cell line), ARH77 (plasma cell leukemia cell line), H2452 (mesothelioma cell line), Karpas-299 (anaplastic large cell lymphoma cell line), and MCF-7 (breast adenocarcinoma cell line). Treatment of peripheral blood mononuclear cells (PBMC) with the extract caused increased production of antitumor cytokines with no change in viability of the cells. In addition, the PBMC treated with the extract has increased cytotoxic activity against chronic myelogenous leukemia cell line. Thus, *C. papaya* exerts antitumor activity through growth inhibitory and immunomodulatory mechanisms. This property could be attributed to the active constituent carpari present in papaya leaves. Papaya leaf also contains a remarkable protein-dissolving enzyme called papain that degrades fibrin that makes up the protective layer of cancer cells, making the cancer cells more susceptible to immune response or chemotherapy. Studies have revealed that mice immunized with papain possess serum antibodies which cross-react with cathepsin-B and cathepsin-H-like endopeptidases isolated from B16 melanoma cells along with inhibition of growth rate, invasion and metastasis in B16 melanoma, and the Lewis lung carcinoma. Thus, the compound hinders tumor growth and prevents it from spreading to other parts of the body. In addition, papaya leaf has antioxidants such as beta-carotene, flavonoids, and vitamin C that scavenge free radicals which are responsible for carcinogenesis, which act as an adjuvant for cancer therapy. Papaya seed has been used for the management of worm infestations in the gastrointestinal tract due to its anthelmintic activity. Papaya seeds contain benzyl isothiocyanate which exhibits antineoplastic effects by inhibiting of carcinogen-activating cytochrome P450 mono-oxygenases and cell cycle progression; inducing carcinogen-detoxifying phase two enzyme and apoptosis. Higher concentration of benzylisothiocyanate has a better inhibition rate of cell proliferation on H69 cell, with IC (50) value of 6.5 μmol/L.

**Tomato**

*Lycopersicon esculentum* or tomato belongs to the nightshade family called Solanaceae. Fleshy fruit of this plant is red in color which is classified based on size and shape as slicing or globe tomato, beefsteak, oxheart, plum, pear, cherri, carpari. Lycopene is the chief active constituent having...
antibiotic, anti-inflammatory, antioxidant, cardiovascular and immunomodulatory effects. Lycopene is a better singlet oxygen scavenger than other carotenoids. Interestingly, tomato leaves have anticancer activity. Extracts of tomato leaves have been shown to exert antineoplastic activity in MCF breast cancer cell lines by causing genetic alterations. Lycopene promotes cell adhesion by increasing E-cadherin expression, reduces cell proliferation by decreasing PCNA expression, and confines proliferating cells to the basal and parabasal layer in 4-nitroquinoline-1-oxide-induced tongue carcinogenesis model in mice. Thus, Lycopene could be used as a chemopreventive agent.

Conclusion

Along with attempts to improve cure rate of cancer, concerted efforts to prevent the disease continuity should be undertaken. This is particularly true for the high-risk population and high-risk individuals. A targeted prevention in high-risk individuals with high-risk lesions using agents targeted to key molecules in the carcinogenesis process should have an impact in lowering the disease morbidity and mortality. Advances in molecular biology have helped to define these high-risk individuals with high-risk lesions and novel chemopreventive targets. In this regard, targeted approach using medicinal properties of plants should overcome some of the earlier setbacks observed in cancer prevention and therapeutic research.

References

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