Review on Functions of Dietary Agents and Plants in Cancer Prevention and Treatment

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ABSTRACT

Over 60% of the current anticancer drugs have their origin from natural sources. Natural products, dietary flavonoids and other polyphenols have an important role as chemo-preventive agents. These substances are compounds with different chemical entities and many of these are present in plants with medicinal value and in various fruits and vegetables commonly consumed by humans. The essential role played by natural products and dietary agents in the discovery and development of effective anticancer agents and the importance of multidisciplinary collaboration in the generation and optimization of novel molecular leads from natural product sources will be reviewed.

Introduction

Cancer is a disease in which disorder occurs in the normal processes of cell division that are controlled by the genetic material (DNA) of the cell. Most of the agents discovered in the first two decades of cancer chemotherapy interacted with DNA and its precursors, inhibiting the synthesis of new genetic material or cause damage to DNA itself.^[1] The process of cancer development is called as carcinogenesis. There are three phases of cancer, first phase is initiation in this carcinogen cause genotoxic damage; second is tumor promotion, in this phase cells undergo rapid proliferation results in accumulation of preneoplastic cells and the final stage is progression phase which involves the growth of tumor with metastatic potential.^[2] Dietary agents are known to modify all these phases. Majority of human cancers results

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Correspondence: Dr. Neelam Singla, E-mail: neelams_singla@rediffmail.com from exposure to environmental carcinogens that include both natural and artificial chemicals, radiations and viruses. Mainly virus, chemical carcinogens, chromosomal rearrangements or spontaneous transformations have been implicated as the cause of cancer. Cancer can occur in different parts of body. The most common cancer in men is lung, prostate or colon cancer where as in women the major ones are breast, lung and colon cancer. The literature indicates that many natural products are available as chemo-protective agents against commonly occurring cancers worldwide.^[3] Despite major scientific and technological progress in combinatorial chemistry, drugs derived from natural products still make an enormous contribution to drug discovery today. An analysis of the number of chemotherapeutic agents and their source indicates that over 60% of the approved drugs are derived from natural compounds.^[4] For e.g. Taxol as a drug has been developed by the National cancer institute, USA and had been approved for the treatment of ovarian, metastatic breast and lung cancer and Kaposi sarcoma. Taxol showed promising results in phase 1 and phase 2 clinical trials conducted in patients of lung, ovarian, breast cancer and squamous cell carcinoma of head and neck. It was originally isolated from the bark of Taxus brevifolia, a finite source of the compound. It binds specifically to the betatubulin unit of microtubule and antagonizes the assembly of cytoskeletol protein.^[5] Another example is vinca alkaloid derived from periwinkle Catharanthus roseus which is found in rain forests of Madagascar had significantly contributed in the treatment of cancer. Vincristine, an alkaloid comstituent of vinca is responsible for increase in cure rate for Hodgkin's disease and some other forms of leukemia. Vincristine inhibits microtubule assembly, including tubulin self association into coiled spiral aggregates at cellular levels.^[6] Etoposide is third exemplary chemoprotective agent derived from plant *Podophyllum peltatum* and *Podophyllum emodi*. It has significant activity against small–cell lung carcinoma. Etoposide is topoisomerase-2 inhibitor, stabilizing enzyme-DNA cleavable complexes leading to DNA breaks.^[7] In addition; the camptothecin derivatives irinotecan and topotecan have shown significant antitumor activity against colorectal and ovarian cancer. These compounds are obtained from bark and wood of *Camptothecea acuminata* and act by inhibiting topoisomerase.^[8] The present work constitutes a review of literature on dietary agents and natural products with potential antitumor activity.

Role of diet in cancer prevention

Eating a balanced diet with plenty of fruits and vegetables helps in reducing the risk of cancer. Higher vegetable consumption will reduce the risk of colon cancer and high fruit consumption can reduce the risk of stomach cancer. Antioxidants and vitamins present in fruits helps in cancer prevention.^[9] The active components of dietary vegetables are responsible for anticancer activity like allicin (Garlic), lycopene (Tomato), soy isoflavones (Soybeans), resveratrol (Grapes), anethole (Fennel), 6-gingerol (Ginger) etc. A major group of these products are the powerful antioxidants, others are phenolic in nature and the remainder includes reactive groups that confer protective properties. These natural products are found in vegetables, fruits plant extracts and herbs, although the mechanism of the protective effect is unclear and the fact that the consumption of fruit and vegetables lowers the incidence of carcinogenesis at a wide variety of sites is broadly supported.^[10] Most of the non-nutrient antioxidants in these foods are phenolic or polyphenolic compounds, such as isoflavones in soybeans, catechins in tea, phenolic esters in coffee, phenolic acid in red wine, quercetin in onions and rosmaric acid in rosemary are responsible for anticancer activity. Many human cancers are prevented by dietary agents.^[1] These are listed in [Table 1].

Natural products and their defense against carcinogenesis

The search for natural products as anticancer agents dates back, at least to the *Ebers papayrus* in 1500 B.C but scientific period of this search becomes more recent with the investigation by Hartwell and co-workers on the application of podophyllotoxin as potential anticancer agent. Plants contain an extensive variety of compounds some of them are extensive modifiers of chemicals carcinogenesis. Many plant extracts and plant derived agents are currently successfully employed in cancer treatment.^[10] These are listed in [Table 2].

Epidemiological studies

In United States, cancer accounts for 25% of the deaths in humans presently. According to the American cancer society, 559,650 deaths were expected from cancer related causes in the year 2007. In addition, 1444920 new cases of cancer will also be diagnosed.^[11] Epidemiological studies also indicated that populations that consume food rich in fruits and vegetables have a lower incidence of cancers. Review of results from 206 human epidemiologic studies has indicated an inverse relationship between consumption of vegetables and fruits and risk for cancers of stomach, esophagus, lung, oral cavity, pharynx, endometrial, pancreases and colon.^[12] Statistics indicate that men are largely

Source	Part	Active component/	Mechanism of action	Cancer inhibited	Ref.
		extract			
Anar (Punica granatum)	Fruit	Ellagic acid, punicic acid, luteolin and caffeic acid	Induces apoptosis	PC-3 human prostate cancer cells	[16]
	Fruit	Extract contaning polyphenols	Induces apoptosis	Breast cancer in mouse mammary organ culture	[17]
Almond (Prunus dulcis)	husk	Terpenoids		MCF-7 human breast cancer cells	[18]
Apple (Pyrus malus)		Extract	Inhibits TNF-alpha induced Nuclear factor kappaB activation.	MCF-7 human breast cancer cells	[19]
Bael (Aegle marmelos)		Hydroalcohlic extract	Induces apoptosis	Ehrlich ascites carcinoma in mice	[20]
Black tea (Camellia sinensis)	Leaves	Decoction	Apoptosis by Bax translocation cytochrome C release and caspase activation	Various tumors	[21]
Brown rice and rice bran (Oryza sativa)	Fermented by aspergillus oryze		Decreases multiplicity of hepatocellular carcinoma	Hepatocellular carcinoma in male F 344 rats	[22]
Clove (Eugenia caryophyllus)		Eugenol	Reactive oxygen speices mediated apoptosis	HL-60 human promylenocytic leukemic cells	[23]
Green tea (Thea sinensis)	Leaves	Epigallocatechin 3-gallate	Catalyzes oxidative DNA cleavage	Various tumors	[24,25]
Grapes (Citrus paradise) See	Seed extract	a) Proanthocyanidins.	GI phase cell cycle arrest and increase in Ci P1/P2 protein level	HT29 human colorectal cancer cells	[26]
		b) Proanthocyanidin B 2-3-3'-di-O-gallate.	Apoptotic death and growth inhibition	DU145 human prostate cancer cells	[27,28]
Garlic (Allium sativum) Bult	Bulbs	S-allyl cysteine	Restoration of E-cadherin expression at transcription and protein level	Human androgen independent prostate cancer	[29]
		Diallyl trisulphide	Increase in caspase -3 activity and inhibition of tubulin proliferation	Human colon cancer	[30]
		Allicin	Accumulation of cells in G0/G1 Phase and cause drop in glutathione level	Human breast, endometrial and colon cancer	[31]

Table I: (Continued)					
Source	Part	Active component/ extract	Mechanism of action	Cancer inhibited	Ref.
Ginger (Zingiber officinalis)	Rhizome	Pungent principles: Vallinoids, (6)-gingerol, shogaols and zingerone.	Induces apoptosis	Various tumors	[32,33]
Lemon (Citrus limonoids)	Seeds and molasses	Limonoids	Enhace chromosomal abnormalities and induces caspase 3/7 activity	Human neuroblastoma and colonic adenocarcinoma cells	[34]
Kalmegh (Andrographis paniculata)		Andrographolide	Cell cycle arrest at G0/G1 phase and enhance production of tumor necrosis factor	HT-29 colon cancer cells	[35]
Mulberry (Morus alba)		Cyaniding 3-rutinoside and cyaniding 3- glucoside	Decrease expression of matrix metalloprotinase -2 (MMP-2) and urokinase plasminogen activator	A-549 human lung carcinoma cells	[36]
Mango (Mangnifera indica)	Juice	Juice extract	Inhibition of cell cycle at G0/G1 phase	HL-60 cells	[37]
Mandarin oranges (Citrus reticulata)		Extract	Induces apoptosis	Sarcoma 180 cells and hepatic cancer cell lines	[38]
Pudina (Mentha piperata)	Leaves	Aqueous extract	Decrease level of lipid peroxidation and increase glutathione content and cause caspase activation	Chemoprotection in benzo[a] pyrene induced lung cancer in swiss albino mice	[39]
Pumpkin (Cucurbita moschata)	Seeds	Moschatin	Ribosomes inactivation and inhibit growth of melanoma cells M-21	Various tumors	[40]
Red- spinach (Amaranthus gangeticus)		Aqueous extract	•	Liver cancer cell lines and MCF-7 breast cancer cells	[41]
Soybeans (Glycine max)		Soy spingolipids	Affect gene expression and cause decrease in m -RNA expression of transcription factors	Colon carcinoma	[42]
		Isoflavones	Cell cycle arrest	Human breast cancer cells	[43]
		Isoflavones	Prevent progression of spontaneous tumors	Hormone refractory prostate cancer in lobund wister rats	[44]
Saffron (Crocus sativus)	Stigma	Carotenoids	Inhibits DNA synthesis	Various tumors	[45,46]
Spinach (Spinacea oleracea)		Sulfoquinovosyl diacyl glycerol	Cell growth suppression	Various tumors	[47]
I	Leaves	Antioxidant	Inhibits cellular proliferation and reduction on number of reactive oxygen speices	Prostate cancer cell lines	[48]
Tomato (Solanum lycopersicum)		Lycopene	Decrease activity of MMP-2 and 9 and inhibit cell growth in dose dependent manner	SK-Hep I human hepatoma cells	[49]
	Tomato paste	Hexane extracts and lycopene	Inhibits cell growth in dose dependent manner and there is increase in level of 8- hydroxydeoxyguanosine/deoxyguanosine	LNCaP human prostate cancer cells	[50,51]
Turmeric (Curcuma	Rhizome	Curcumin	Inhibition of transcription factor NF-kappaB	Pancreatic cancer	[52,53]
longa)		Curcumin	Inhibits proliferation of both IFN alpha- sensitive and IFN alpha- resistant cancer cells in bladder	Bladder cancer	[54]
Wheat germ			Reduces chemotherapy induces febrile neutropenia	Pediatric cancer	[55]

Table 2: Herbs and natural products for cancer prevention					
Plant name	Part	Active component/extract	Mechanism of action	Cancer inhibited	Ref.
Azadiracta indica	Leaves	Aqueous leaf extract	Decrease in oxidative stress and increase in glutathione content that leads to apoptosis	Skin tumor in male balb/c mice	[56]
		Ethanolic leaf extract	Decrease expression of PCNA, mutant p 53 and Bcl -2	Hamster buccal pouch carcinoma	[57]
		Ethanolic leaf extract	Lipid peroxidation and enhances antioxidant status of stomach.	Gastric carcinoma	[58]
Amoora dasyclada	Twigs	3α-acetoxy-24,25,26,27 tetranortirucalla-7-ene		Human liver cancer cells	[59]
Agalia elliptifolia		Rocoglamide	Inhibits TNF-alpha or PMA induced NF- kappaB activity in T-lymphocytes and induce apoptosis	Human cancer cell lines s	[60]
Aralia nudicaulis	Rhizomes	Hexane extract		Human colon cancer cells and human leukemic cells	[61]
	Fruit	Hexane extract		Human cervix cancer cells	[61]
Aglaia crassinervia	Bark	Rocaglaol	Induces apoptosis of LNCaP cells and G2/M phase cell cycle arrest	Various cancer	[62]
Alstonia scholaris		Alkaloid fraction	Induces apoptosis	HeLA, Hep G (2), KB, HL- 60, MCF-7 cancer cells	[63]
Artemisia sylvatica	Aerial parts	Sesquiterpenes from methanol extract	Inhibitory effect on LPS- induced NF-kappaB	Various cancers	[64]
Artemisia princep		Yomogin	Causes activation of caspase -3 and induces apoptosis	HL-60 human promylenocytic leukemic cells	[65]

(Continued)

Table 2: (Continued)					
Plant name	Part	Active component/extract	Mechanism of action	Cancer inhibited	Ref.
Angelica sinensis		n-butylidenephthalide from chloroform extract	Up regulation of expression of cyclin kinase inhibitor and cause cell cycle arrest at G0/G1 phase.	Malignant brain tumor	[66]
		Acetone fraction	Decrease number of cells in S-phase and induces apoptosis	A-549, HT-29, JS human cancer cells	[67]
Annona glabra		Cunabic acid (diterpene)	Arrest at G0/GI phase and induces apoptosis by down regulating the gene expression of Bcl-2 gene	SMMC-7721 human liver cell line	[68]
Aglaia silvestris	Fruits and twigs	Silvestrol and episilvestrol	- T 0	Human oral epidermoid carcinoma cell line	[69]
Arisaema tortuosum	Tubers	Lectin		HT-29, OVCAR-5, SiHa human lung cancer cell lines	[70]
Avicennia germinans	Leaves and twigs	3-chloro deoxylapachol		KB human cancer cells	[71]
Annona reticulata	Seeds	Squamocin	Induces expression of Bax and enhances caspase-3 activity	T-24 bladder cancer cells	[72]
Alvaradoa haitiensis	Leaves	Alvaradoin E	Chromatin condensation	Various tumors	[73]
Bamboo	Leaves	201-hydroxy purpurin-7 δ lactone ethyl methyl diester from methanolic extract	Induces apoptosis.	CMK-7 human leukemic cell lines	[74]
Bischofia javanica	Bark	Betulic acid and its derivatives	DNA topoisomerase II inhibitors	Various tumors	[75]
Betula platyphylla		Methanolic extract	Increases cell viability against water and induces apoptosis	Hamster lung fibroblast cell lines	[76]
Calotropis procera	Latex	Methanolic extract	Decrease in Serum vascular endothelial growth factor and cause cell death in hepatoma and non hepatoma cell lines.	Hepatocellular cell lines.	[77]
Clematis manshrica		Saponins		Sarcoma-180, Hep A and P-388 cancer cell lines.	[78]
Chamaecyparis nootkatensis		Diterpenes		Various cancers	[79]
Coptis japonica	Root	Methanol extract	Induces apoptosis through caspase -3 activation	SNU-688 human gastric cancer cells.	[80]
Capaifera multijuga		Oil resin		Melanoma cell line	[81]
Capparis sikkimensis		Cappamensin A		Ovarian (1A-9), lung (A-549), Breast (MCF-7) cancer cell lines	[82]
Digitalis purpurea	Leaves	Gitoxin and gitoxigenin	Induces apoptosis	TK-10 renal adenocarcinoma cancer cells	[83]
Dioscorea futschauensis	Rhizomes	Pentacyclic triterpenoid glycoside	Induces apoptosis by mitrocondrial controlled apoptotic pathway	HCT human colon carcinoma cells	[84]
Dioscorea bulbifera		Petroleum ether extract		Chemoprotection in mice	[85]
Dendrobrium loddigesii	Stoms	Moscatilin	C2 phase arrest	Various cancers	[86]
Dioscorea collettii	Rhizomes	Steroidal saponins(methyl protoneogracillin and gracillin)		Leukemic , Prostate and CNS cancer cells	[87]
Evodia fructus		Evodiamine	Causes G2/M phase areast and cause tubulin polymerization and promotes phosphorylations of kinase and Bcl-2	Human multiple drug resistant breast cancer cells	[88]
Evodia ruteacarpa	Fruits	Quinolone compounds	Inhibitory activity on nuclear factor of activated T–cells	Various cancers	[89]
Gymnocladus chinensis baillon	Fruit	Triterpenoid saponin	Induces apoptosis and causes inactivation of NF- kappaB	Various cancers	[90]
Garcinia hanburyi		Gambogic acid and epigambogic acid		Human leukemic K-562 and doxorubicin resistant K-562/R cell lines	[91]
Ginkgo biloba		Extract	Decreases peripheral type benzodiazepine receptor levels and induces apoptosis	MDA-MB-231 breast cancer cell lines and U-87 glioma cell lines	[92]
Geum quellyon sweet	Roots	Tannins	Necrosis cell death and apoptotic cell death	Colon adenocarcinoma, oral squamous and androgen insensitive prostate cancer cells	[93]
Hibiscus sabdariffa	Dried calicus	Delphidin 3-sambubioside	Elevation of intracellular reactive oxygen speices and cause activation of caspase 3, 8 and 9	Human leukemic cells	[94]
Kaempferia parviflora	Rhizomes	Flavone derivatives from ethanol extract	Increase accumulation of rhodamine 123 and	Increase oral bioavailability	[95]
Lindera strychifolia	Roots	Extract	Induces apoptosis	A-549 and SBC-3 human lung cancer cell line	[96]

(Continued)

Table 2: (Continued)					
Plant name	Part	Active component/extract	Mechanism of action	Cancer inhibited	Ref.
Lycium barbarum		Polysaccharide	Cause cell cycle arrest in S phase and apoptosis induction	QGY7703 human hepatoma cells	[97]
Morinda citrifolia	Fruit	Polysaccharide rich compounds		Sarcoma 180 ascites tumour in mice	[98]
Miliusa sinensis	Flowers	Miliusanes		MCF-7, COL-2, Lu -1, LNCap cancers cells	[99]
Oledenlandia diffusa		Water extract	Pro apoptotic effect	Effect on lung metastases	[100]
Phyllanthus urinaria		Extract	Increaseof apoptosis in tumour sections.	Lewis lung carcinoma	[101]
D		Aqueous extract	Induces apoptosis in human cancer cells	Human cancer cells	[102]
Partinia villosa Plumeria bicolor	Leaves bark	Flavones Plumeridepentaacetate obtained from methanolic extract		K-562 cancer cells Various cancers	[103] [104]
Parinari sprucei	Leaves	Kaurene type diterpenoids		Various cancers	[105]
Platycodon grandiflorum	Roots	Petroleum ether extract		Various cancers	[106]
Pterocarpus santalinus		Methanolic extract	Chromatin condensation and sub GI phase accumulation	Human cervical adenocarcinoma cell line	[107]
Pinus maritima	Bark	Phenolic compounds containing extract		Skin carcinoma	[108]
Peganum hermala		Harmine alkaloids	Inhibits expression of Bcl-2 gene and significantly induces apoptosis	Various cancers	[109]
Pistacia lentiscus		50% ethanol extract	Cell cycle arrest at G1 phase and cause activation of caspase -3, 8 and 9	HCT116 human colon cancer cells	[110]
Rhus verniciflua		Flavanoids	Growth inhibition and apoptosis in HOS cells, activation of caspase -3 and Bax activity	Hepatic cell line in mouse /	[111]
Rhodiola rosea	Rhizomes	Extract	Apoptosis from G2/M phase of cell cycle and cause necrosis in HL-60 cells	Cytotoxic to HL-60 cells	[112]
Sequia sempervirens	Leaves	Norlignans(agatharesinol acetonide)		A-549 non- small- lung cancer cell line	[113]
Scutellaria baicalensis	Roots	Flavanoids	Inhibits growth in recurrent and drug resistant brain tumor cell lines	Various cancers	[114]
		Baicalein/wogonin/ neobaicalein	Causes cell cycle changes and shows antiandrogenic effect	Prostate cancer	[115]
Scatellariae radix Saurures chinensis		5,6,7 trimethyl baicalein Neolignans	Cell cycle arrest Cell cycle arrest at G1 phase and cause dow	Hepatocellular carcinoma nPC-3 prostate cancer cells	[6] [7]
Sauda munaid			regulation of Bcl-2 and upregulation of Bax		F1 1 01
Suvuu munziu		Aqueous extract	dependent inhibition of protein , DNA and RNA synthesis	cells	[II0]
Silibium marium		Silibin	G1 and G2/M phase arrest and inhibits CDK2,CDK4 kinase activity in hepatic cells	Human hepatocellular carcinoma	[119]
		Silibin	Reduces expression of MMP-2 and urokinase plasminogen factor activator	e Human lung cancer cells	[120]
Solanum nigrum		150 –kDa glycoprotein	Inhibits protein kinase C alpha translocation and NO production	Carcinogenic to HCT-116 cells	[121]
Toddalia asiatica		Dihydronitidine		A-549 cells	[122]
Tinospora cordifolia		Dichloromethane extract	Depletion of glutathione concentration and increase in lipid peroxidation	Ehrlich ascites carcinoma of mice	[123]
Tribulus terrestris	Fruits	Steroidal glycosides		SK-MEL human malignant melanoma cell	[124]
Toona sinensis		Aqueous extract	Apoptosis accompanied by release of cytochrome C and caspase 3-activation	Human premyelocytic leukemic cells	[125]
Uvaria hamiltonii Voodoo lily	Tubers	Aurone 20 Lectin alkaloids	G2/M phase cell cycle arrest	Anticancer agent Antiproliferative activity	[126] [127]
(sauromatum venosum Viscum coloratum		Lectin alkaloids	Caspase 3 activation, lectin - 11 induced apoptosis, enhancement of cytokinin release	U-937, HL-60, lymphoblastoid cells and	[128]
Viscum album		Extract	Induces apoptosis and necrosis	hepatocarcinoma cells Colorectal cancer	[129]
Vitex trifolia		Flavonoids	Cause cell cycle arrest at G2/M and G0/G1	Mammalian cancer cells	[130]
Ximonia Amoricana		Riprovimin	pnase Inhibits ribosomos protoin	Antinoonlastic agent	[121]
Aimenia Americana		Aqueous extract	ninibits ribosomes protein	CC531 rat colorectal	[131]
Youngia japonica		Aqueous extract		Human myelogenous leukemia	[133]
Zanthoxylum madagascariense	Stem bark	Cyclohexane extract (benzophenanthridine type alkaloids)	Cell cycle arrest in G0/G1 phase as well as decrease of cells in S – phase	Human colorectal adenocarcinoma.	[134]

plagued by lung, colon, rectum and prostrate cancer. Recent United States study was conducted involving 628 men under the age of 65 years with newly diagnosed prostrate cancer.^[1] A large study involving 35,000 non-smokings, mainly vegetarian, Seventh Day Adventists found a reduced risk of lung, prostrate, pancreas and colon cancers.^[9] Women in Japan and the Far East have a much lower incidence of breast cancer than women in the West. These women have a high consumption of soy products containing isoflavones, which are phytoestrogen or plant estrogen.^[13] The changing profiles in the incidence of certain cancers in South Africa have been attributed to urbanization, with increased consumption of meat, refined carbohydrates, alcohol and smoking. The rural African diet of Soy and vegetables was a perfect combination of protein and complex carbohydrates with adequate fiber and plant nutrients.^[14] The epidemiological evidence suggests protection against a wide array of cancers, particularly those of the respiratory and digestive tracts and to a lesser extent the hormone-related cancers.^[15]

Conclusion

This paper has discussed role of diet and natural products in the treatment of cancer. Diet rich in vegetables, fruits and legumes contains large amount of antioxidants that protect against the deleterious actions of free radicals that may lead to cancer development. Experimental agents derived from natural sources are offering us a great opportunity to evaluate not only totally new chemical class of anticancer agents, but also with novel and potential mechanism of action. So it is no longer an option to ignore plants and dietary agents or treat them as something unconventional from regular medical practice. The challenge put before this system of medicine is to move forward carefully, using both reasoning and wisdom.

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