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Natural products for cancer prevention: a global perspective

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Abstract

The control of cancer, the second leading cause of death worldwide, may benefit from the potential that resides in alternative therapies. The primary carcinogens stem from a variety of agricultural, industrial, and dietary factors. Conventional therapies cause serious side effects and, at best, merely extend the patient's lifespan by a few years. There is thus the need to utilise alternative concepts or approaches to the prevention of cancer. This review focuses on the many natural products that have been implicated in cancer prevention and that promote human health without recognisable side effects. These molecules originate from vegetables, fruits, plant extracts, and herbs.

Keywords: Cancer prevention; Natural products; Plants; Anticancer; Chemoprotection

Abbreviations: BBI, bisbenzylisoalkaloids; IC_{50}, fifty percent inhibitory concentration; i.p., intra-peritoneal.

Contents

1. Introduction

Mortality that results from the common forms of cancer is still unacceptably high. Despite many therapeutic advan-

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ces in the understanding of the processes in carcinogenesis, overall mortality statistics are unlikely to change until there is a reorientation of the concepts for the use of natural products as new chemopreventive agents. Natural or semi-synthetic compounds may be used to block, reverse, or prevent the development of invasive cancers. Cellular carcinogenesis forms the biologic basis for the identification of preventive products, the assessment of their activity, and ultimately the success or failure of a therapy.

As long ago as 480 BC, Hippocrates recognised that several aspects of what we now call "lifestyle" must come together to produce a healthy body. He said, "Positive health requires a knowledge of man's primary constitution and the powers of various foods, both those natural to them and those resulting from human skill." What Hippocrates called "man's primary constitution," we today call "genetics," and we can infer that foods "resulting from human skills" can be equated with today's diet.

Cancers may be caused in one of three ways, namely incorrect diet, genetic predisposition, and via the environment. At least 35% of all cancers worldwide are caused by an incorrect diet, and in the case of colon cancer, diet may account for 80% of the cases. When one adds alcohol and cigarettes to their diet, the percentage may increase to 60%. Genetic predisposition to cancer lends itself to ~20% of cancer cases, thus leaving the majority of cancers being associated with a host of environmental carcinogens. Doll and Peto (1981) reported that in the United States the major environmental carcinogens include air and water pollution, radiation, and medication.

2. Cancer

2.1. Carcinogens

The majority of human cancers result from exposure to environmental carcinogens; these include both natural and manmade chemicals, radiation, and viruses. Carcinogens may be divided into several classes, as shown in Table 1. (1) Genotoxic carcinogens, if they react with nucleic acids. These can be directly acting or primary carcinogens, if they are of such reactivity so as to directly affect cellular constituents. (2) Alternatively, they may be procarcinogens that require metabolic activation to induce carcinogenesis. (3) Epigenetic carcinogens are those that are not genotoxic. Molecular diversity of the cancer-initiating compounds ranges from metals to complex organic chemicals (Fig. 1), and there is large variation in potency. The variation in structure and potency suggests that more than one mechanism is involved in carcinogenesis.

It is also clear that apart from exposure to carcinogens other factors such as the genetic predisposition have been documented. Thus, patients with the genetic xeroderma pigmentosum are more susceptible to skin cancer. Furthermore, incidence of bladder cancer is significantly higher in those individuals who have the slow acetylator phenotype, especially if they are exposed to aromatic amines.

Table 1
Types of carcinogens (Timbrell, 2000)

Type	Example
1. Genotoxic carcinogen	
Primary, direct-acting alkylating agents	Dimethylsulfate, ethylene imine, β-propiolactonel
2. Procarcinogens	
Polycyclic aromatic hydrocarbons	Benzo[*a*]pyrene
Nitrosamines	Dimethylnitrosamine
Hydrazine	1,2-Dimethylhydrazine
Inorganic	Cadmium, plutonium
3. Epigenetic carcinogens	
Promotors	Phorbol esters, saccharin, bile acids
Solid state	Asbestos, plastic
Hormones	Estrogens
Immunosuppressants	Purine analogues
Cocarcinogens	Catechol
4. Unclassified	
Peroxisome proliferators	Clofibrate, phthalate esters

Carcinogens in the diet that trigger the initial stage include moulds and aflatoxins (for example, in peanuts and maize), nitrosamines (in smoked meats and other cured products), rancid fats and cooking oils, alcohol, and additives and preservatives. A combination of foods may have a cumulative effect, and when incorrect diet is added to a polluted environment, smoking, UV radiation, free radicals, lack of exercise, and stress, the stage is set for DNA damage and cancer progression. On the protective side, we know that a diet rich in fruit, vegetables, and fibre is associated with a reduced risk of cancer at most sites.

2.2. Cell cycle

Cancer is a disease in which disorder occurs in the normal processes of cell division, which are controlled by the genetic material (DNA) of the cell. Viruses, chemical carcinogens, chromosomal rearrangement, tumor suppressor genes, or spontaneous transformation have been implicated in the cause of cancer. For a cell to replicate, it must (1) faithfully reproduce its DNA, (2) manufacture sufficient cellular organelles, membranes, soluble proteins, etc., to enable the daughter cells to survive, and (3) partition the DNA and cytoplasm (containing organelles) equally to form two daughter cells. This process requires a significant amount of feedback control to ensure that the molecular steps are sequential and correctly orientated. Failure to control the cell cycle process carries with it a high price. Higher eukaryotes have a "dead man's handle" safety system, whereby their basic life program undergoes apoptosis.

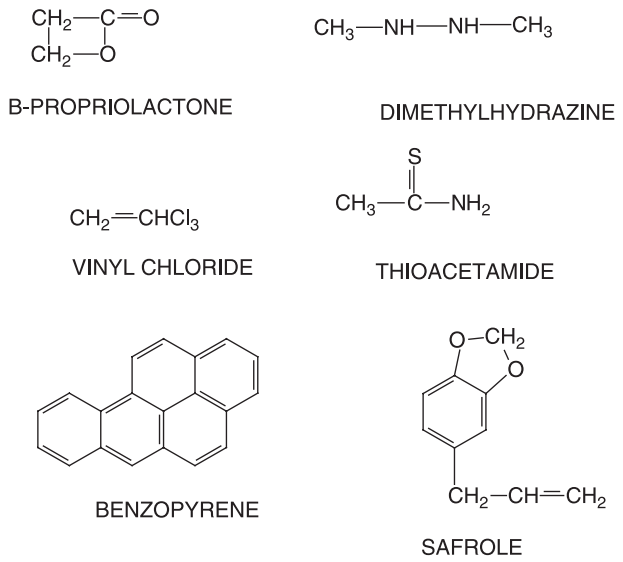

Fig. 1. Structures of various carcinogens (Timbrell, 2000).

2.3. Carcinogenesis

The transformation of a normal cell into a cancerous cell is believed to proceed through many stages over a number of years or even decades. The stages of carcinogenesis include initiation, promotion, and progression. The first stage involves a reaction between the cancer-producing substance (carcinogen) and the DNA of tissue cells. There may be a genetic susceptibility. This stage may remain dormant, and the subject may only be at risk for developing cancer at a later stage. The second stage occurs very slowly over a period ranging from several months to years. During this stage, a change in diet and lifestyle can have a beneficial effect so that the person may not develop cancer during his or her lifetime. The third and final stage involves progression and spread of the cancer, at which point diet may have less of an impact. Preventing initiation is an important anticancer strategy, as are the opportunities to inhibit cancer throughout the latter stages of malignancy.

One of the most important mechanisms contributing to cancer is considered to be oxidative damage to the DNA. If a cell containing damaged DNA divides before the DNA can be repaired, the result is likely to be a permanent genetic alteration constituting a first step in carcinogenesis. Body cells that divide rapidly are more susceptible to carcinogenesis because there is less opportunity for DNA repair before cell division. Mutagenic changes in the components of signalling pathways lead to cellular transformation (cancer).

2.4. Global cancer incidence

Modern man is confronted with an increasing incidence of cancer and cancer deaths annually. Statistics indicate that men are largely plagued by lung, colon, rectum, and prostrate cancer, whilst women increasingly suffer from breast, colon, rectum, and stomach cancer (Abdulla & Gruber, 2000).

3. Epidemiological studies

A recent United States study was conducted involving 628 men under the age of 65 years with newly diagnosed prostrate cancer. They were placed on a trial of fruit and vegetables for 5 years. It was found that while fruit was not protective, vegetables, especially cruciferous vegetables (cabbage, broccoli, brussel sprouts, and cauliflower), reduced risk. Tomatoes containing lycopene are protective against prostrate cancer, and when α-tocopherol (a variety of vitamin E) is added to lycopene, prostrate cancer progression may be curtailed by almost 90% (Klein et al., 2001). Other research has found that plant sterols and sterolins found in pumpkinseeds, the African potato, and some vegetables have a beneficial effect on prostrate health.

A large study involving 35,000 nonsmoking, mainly vegetarian, Seventh Day Adventists found a reduced risk of lung, prostrate, pancreas, and colon cancers. Antioxidant vitamins also help to fight the damage caused by harmful stomach bacteria and are protective (Pryor et al., 2000). The low incidence of large bowel cancers in India can be attributed to their diet high in carbohydrates and natural antioxidants, including turmeric. Animal studies have shown that squalene, found in olive oil, inhibits colon, lung, and skin cancers. A Japanese study found that the probiotic *Lactobacillus* (found in yogurt) can delay the onset of cancer by enhancing the activity of natural killer cells, which are the particular white blood cells responsible for attacking foreign invaders.

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. Phytoestrogens bind the estrogen receptors in the body and therefore block the cancer-promoting effects of estrogen. Researchers from the University of Texas supplemented the diet of women with isoflavones contained in soymilk, and this reduced estrogen levels by 25% and progesterone levels by 45%. Plant estrogens are also found in red clover, black cohosh, rhubarb, and flaxseed and are highly recommended to reduce breast and prostrate cancer (Demark-Wahnefried et al., 2001).

The changing profiles in the incidence of certain cancers in South Africa has been attributed to urbanisation, with increased consumption of meat, refined carbohydrates, alcohol, and smoking. The rural African diet of samp, beans, and vegetables was a perfect combination of protein and complex carbohydrates with adequate fibre and plant nutrients. This has given way to white bread, jam, soft drinks, and fast foods. The cause of esophageal cancer, so

Table 2
Epidemiological studies of fruit and vegetable intake and cancer prevention

Cancer site	Number of studies	Significant protective effects	Significantly increased risk
All sites including prostate	170	132	6
All sites except prostate	156	128	4
Lung	25	24	0
Larynx	4	4	0
Oral cavity, pharynx	9	9	0
Esophagus	16	15	0
Stomach	19	17	1
Colorectal	27	20	3
Bladder	5	3	0
Pancreas	11	9	0
Cervix	8	7	0
Ovary	4	3	0
Breast	14	8	0
Prostrate	14	4	2
Miscellaneous[1]	8	6	0

[1] Melanoma, thyroid, biliary tract, mesothelioma, endometrial, and childhood brain tumors (Langset, 1995).

common in the Transkei, has eluded scientists for decades. It has been postulated that possible causes could be aflatoxins (toxins manufactured by detrimental fungi that often grow on foods) found in maize or a mineral deficiency in the soil. Another carcinogenic chemical is dioxin, which enters the food chain when animals eat contaminated plants. When humans consume meat, dairy products, and fish, they ingest a highly concentrated load of dioxin, which has been linked to several cancers. A recent study indicated that woman who ate healthy diets were 30% less likely to die than those who did not. South African blacks have a lower incidence of colon cancer than whites, which was found to be due to a lower intake of animal protein and fat (O'Keefe et al., 1999). Epidemiological studies involving various human cancer sites indicate that fruit and vegetable intake significantly protects against cancer (Table 2).

4. Natural products and defense against carcinogenesis

The literature indicates that many natural products are available as chemoprotective agents against commonly occurring cancers occurring worldwide. 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 (Table 3), plant extracts, and herbs (Table 4). Although the mechanism of the protective effect is unclear, the fact that the consumption of fruit and vegetables lowers the incidence of carcinogenesis at a wide variety of sites is broadly supported. The epidemiological evidence suggests protection against a wide array of cancers (Table 2), particularly those of the respir-

Table 3
Chemoprotective antioxidants from fruits vegetables

Source	Active component	Mechanism of action	Cancer inhibited (reference)
Olives	Polyphenols	Antioxidant	Various cancers (Langset, 1995)
Apples		Antioxidant	Various cancers (Eberhardt et al., 2000)
Strawberries, cantaloupe, melon	Vitamin C, bioflavonoids, chalcones	Antioxidant	Various cancers (Paiva & Russell, 1999)
Leafy greens, cabbage, broccoli, cauliflower	Vitamin C, lutein and zeaxanthin	Scavenger of ROS, antioxidant, suppresses promotion of lung tumors in mice	Various cancers; crypt foci in SD rat colon (Abdulla & Gruber, 2000; Ceruti et al., 1986; Nishino et al., 2000; Rauscher et al., 1998; Stahl et al., 2000)
Vegetables oils, cold-pressed seed oils, wheat germ	Vitamin E	Protects against lipid peroxidation	Skin cancer (Paiva & Russell, 1999; Stahl et al., 2000)
Yellow-orange vegetables and fruits	β-Carotene	Antioxidant	Various cancers (Paiva & Russell, 1999; Stahl et al., 2000)
Carrots	α- and β-carotene, phenolic compounds	Antioxidant, pS2 gene expression, α-carotene more effective, inhibits tumors in rats and mice	Pancreatic, colon, breast cancer; liver cells; rat, mice colon and liver cancer (Cheng et al., 2001; Eberhardt et al., 2000; King et al., 1997; Nishino et al., 2000)
Tomatoes	Lycopene, vitamin C	Strong antioxidant, inhibits lymphocyte DNA-oxidated damage	Leukemia, lung cancer; mice tumors (Giovannucci, 1999; Hecht et al., 1999; Kim et al., 2000a; Watzl et al., 1999)
Grapes, red wine	Phenols, catechins	Antioxidant	Various cancers (Abdulla & Gruber, 2000)
Citrus fruits	β-Cryptoxanthin, bioflavonoids, chalcones, vitamin C	Antioxidant, stimulates expression of RB gene and p73 gene (a p53-related gene)	Rat tumors; various cancers (Nishino et al., 2000)
Garlic, onions, leeks, chives	Allicin, flavonoids, vitamin C, selenium, sulfur	Detoxifies carcinogen, inhibits *Helicobacter pylori*, cell cycle arrest from S to G2M boundary phase	Stomach cancer (Barch et al., 1996; Zheng et al., 1997)
Common bean	Phenolic compounds	Antimutagenic	Aflatoxin-induced cancer (Cardador-Martinez et al., 2002; Galvano et al., 2001)

Table 4
Chemoprotective products found in plant extracts causing molecular changes

Source	Active component	Mechanism of action	Cancer inhibited (reference)
Gymnosporia rothiana Laws	GCE: chloroform ether extract	DNA/RNA and protein synthesis inhibited after treatment for 12–36 hr	Leukemia in mice (Chapekar & Sahasrabudhe, 1981)
Rhizoma zedoariae	β-Elemene	Cell cycle arrest from S to G2M phase	(Yuan et al., 1999; Zheng et al., 1997)
Pinus pinaster, *P. maritime*	Polyphenolic fraction, ferrulic acid, bioflavonoids, proanthocyanidins Procydin (SA), Pycnogenol (Europe)	Antioxidant, improves blood circulation, increases cytokine levels, increases activity of NK cells, modulates mitogenic signaling and induction of G1 arrest and apoptosis	DU145 cells, prostrate, skin cancer (Agarwal et al., 2000)
Viscum album var., *Viscum* var. *coloratum* (Korean mistletoe)	Lectin alkaloids	Caspase-3 activation, lectin 11-induced apoptosis, inhibition of telomerase via mitochondrial controlled pathway independent of p53, enhancement of cytokine release	U937, HL-60, lymphoblastoid cells, hepatocarcinoma cells (Duong Van Huyen et al., 2001; Kim et al., 2000b; Lyu et al., 2001; Park et al., 2001; Ribereau-Gayon et al., 1997)
	Hexamethylene bioacetamide	p53-dependent apoptosis, induction with telomerase activity	Human colon carcinoma LoVo cells, leukemic cells (Zhang et al., 2000)
Azadirachta indica Juss (Neem leaf)	Polyphenolic	Cytotoxic	Various cancers (Gogate, 1991)
Muscadene berries	Resveratrol	Antioxidant	Lung tumor in A/J mice (Hecht et al., 1999)
	myo-Inositol, dexamethasone	Antioxidant	Lung tumor in A/J mice, liver cancer (Hecht et al., 1999; Witschi et al., 1999)
Curcuma longa L. turmeric	Curcumin	Antioxidant	Prostate, lung tumor in A/J mice (Dorai et al., 2001; Hecht et al., 1999; Li & Lin-Shia, 2001)
	Esculetin	Antioxidant	Lung tumor in A/J mice (Hecht et al., 1999)
Acanthopanax gracilistylus (Chinese herb)		Antioxidant	Liver cancer cells (Lin & Huang, 2000)
Cylopia intermedia (honeybush tea)	Polyphenolic compounds	Antioxidant, antimutagenic, interferes with *P*450-mediated metabolism	Various cancers (Marnewick et al., 2000)
Undaria pinnantifida (seaweed)	(Viva-Natural)	Prophylactic	Lewis lung cancer in mice (Furusawa & Furusawa, 1985)
Rosemary, sage, other spices	Carnosic acid, rosemary acid		
Rubia cordifolia	RC-18	Forms DNA adducts	P388 and L1210 cells, B16 melanoma (Adwankar & Chitnis, 1982; Poginsky et al., 1991)
	Valepotriates	Cytotoxic	(Bounthnah et al., 1981)
Scutellariae radix, *S. indica*	Flavonoids	Prostaglandin E_2 production	Rat C6 glioma cells (Nakahata et al., 1998)
Soybeans	Isoflavones, phenolic acids, genistein (piperazine complex)	Protein tyrosine kinase inhibitor, diverse EGFR and p21 *ras* expression phenotypes, dependent on epidermal cell growth factor receptor, estrogen-like action	Jurkat T-leukemia cells, bladder cancer (Abdulla & Gruber, 2000; Polkowski & Mazurek, 2000; Spinozzi et al., 1994; Theodorescu et al., 1998)
Various plants	Quercetin, kaempferol, rutin, hesperidin	OH scavenger	B16 melanoma (Day et al., 2000; Drewa et al., 2001)
Camellia sinensis, green tea, black tea	Polyphenols, epigallocatechin-3-gallate	Apoptosis induction, cell cycle arrest	Tumor cells (Ahmad et al., 1997; Zhao et al., 1997)
Apalathus linearis (unfermented rooibos tea)			
Coriolus versicolor (Chinese herb)	Bis-benzylisoalkaloids, bufalin, berberine, tetrandrine	Apoptosis induction, complexes with DNA	HL-60, U937 cells (Dong et al., 1997; Jing et al., 1994; Kuo et al., 1995)
Uncaria tomentosa		Apoptosis induction	Tumor cells (Sheng et al., 1998)
Eucalyptus grandis	Euglobal-G1		Various cancers (Takasaki et al., 2000)
Ornithogalum	Cholestane glycoside	Apoptosis induction	HL-60 cells (Hirano et al., 1996)

atory and digestive tracts and to a lesser extent the hormone-related cancers. A host of plant constituents could be responsible for the protective effects, and it is likely that several of them play a role under some circumstances. Most of the nonnutrient 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.

Of the many anticarcinogens already detected in plant foods, the antioxidants vitamins C and E and the provitamin β-carotene have received the most attention (Handelman, 2001). Although there has been considered enthusiasm for the potential anticarcinogenic properties of β-carotene,

research findings suggest that several different carotenoids are likely to be associated with reduced cancer risks. In two intervention trials to investigate the potential protective effects of β-carotene against cancer, an unexpected significantly higher incidence of lung cancer was found in men taking supplements compared with those not taking additional β-carotene. These men were long-time heavy smokers and may represent a special case in that their lung cancer may have been initiated many years before the study took place (Michaud et al., 2000). These results cause concern and need serious consideration. They do not invalidate the concept of the importance of antioxidant nutrients but do underline the need to examine the relative influence of supplements of a single antioxidant nutrient (as distinct from complex mixtures of antioxidants in foods) as well as interactions between the effects of smoking, antioxidant nutrients, and disease progression.

A number of naturally occurring compounds from vegetables and herbs exert chemopreventive properties against carcinogenesis. Most studies appear to test the natural products on human leukemia cells. The Chinese medicinal herb *Rhizoma zedoariae*, for example, produces a compound called lemene, which has been shown to exhibit antitumor activity in human and murine tumor cells in vitro and in vivo (Zheng et al., 1997). The IC_{50} values of lemene indicated severe inhibition of promyelocytic HL-60 cells, erythroleukemia K562 cells, and especially peripheral blood leukocytes. This was associated with cell arrest from S to G2M phase transition and with induction of apoptosis (Yuan et al., 1999). Similar inhibitory effects were produced by allicin, a natural organosulfide from garlic. In vitro inhibition of proliferation of HL-60 cells or induction of apoptosis in promyelocytic leukemia was also demonstrated by Dong et al. (1997) using other Chinese medicinal products, namely the bis-benzylisoquinoline alkaloids, tetrandrine and berberine, by Jing et al. (1994) using bufalin, by Sheng et al. (1998) using extracts of *Uncaria tomentosa*, and by Hirano et al. (1996) using cholestane glycosidase.

5. Mechanisms of action of natural products on carcinogenesis

In the last decade, advances in cancer research have enhanced our understanding of cancer biology and genetics. Among the most important of these is that the genes that control apoptosis have a major effect on malignancy through the disruption of the apoptotic process that leads to tumor initiation, progression, and metastasis. Therefore, one mechanism of tumor suppression by natural products may be to induce apoptosis (Table 4), thereby providing a genetic basis for cancer therapy by natural products.

The p53 protein, encoded by a tumor suppressor gene, mediates growth arrest or apoptosis in response to a variety of stresses. p53-Dependent apoptosis, occurring in several sensitive tissues after radiation or chemotherapy, is partially responsible for the side effects of cancer treatment, making p53 a potential target for therapeutic suppression. Hypoxic stress, such as DNA damage, induces p53 protein accumulation and p53-dependent apoptosis in oncogenically transformed cells. Unlike DNA damage, hypoxia does not induce p53-dependent cell cycle arrest, suggesting that p53 activity is differentially regulated by these two stresses. Genotoxic stress induces both kinds of interactions, whereas stresses that lack a DNA damage component, as exemplified by hypoxia, primarily induce interaction with cosuppressors. However, inhibition of either type of interaction can result in diminished apoptotic activity. Germ line mutations of the p53 tumor suppressor gene in patients with a high risk for cancer inactivate the p53 protein (Colic & Pavelic, 2000). Lung-specific expression of the p53 and K-*ras* genes in mice was reported by Witschi et al. (1999), Brockman et al. (1992), and Wattenberg and Estensen (1996), when mice were exposed to natural products, such as *myo*-inositol, dexamethasone, curcumin, esculetin, resveratrol, lycopene, and butylated hydroxyanisole. The question whether any of the known natural products modulate expression of the p53 protein requires experimentation (Mann, 2002).

Carcinogens in the diet that trigger the initial stage include moulds and aflatoxins (for example, in peanuts and maize), nitrosamines (in smoked meats and other cured products), rancid fats and cooking oils, alcohol, and additives and preservatives. A combination of foods may have a cumulative effect, and when incorrect diet is added to a polluted environment, smoking, UV radiation, free radicals, lack of exercise, and stress, the stage is set for DNA damage and cancer progression. In addition to the usual vitamin and mineral supplements, amino acids such as cysteine and natural antioxidants such as clove oil constituents are particularly helpful in offsetting problems caused by a variety of environmental toxins.

Many diseases, including cancer, have been shown to be linked to a poorly functioning liver detoxification system. A study at an Italian chemical plant showed that workers with an inadequate liver detoxification enzyme later developed bladder cancer. Herbs that promote a healthy liver function include dandelion (taraxacum), milk thistle (silybum), and artichoke (cynara). Beetroot is particularly beneficial and may be eaten raw, cooked, or in juices. Raw vegetable juices, which may include carrots, celery, and parsley, together with beetroot are an excellent way of providing concentrated antioxidants and plant enzymes (Stahl et al., 2000). Wheat grass is also useful. A diet rich in cruciferous vegetables and vitamins B (in whole grains and cereals) and C (cabbage, broccoli, and brussel sprouts) promotes liver detoxification. Other vitamin C foods are peppers, tomatoes, oranges, and tangerines. Glutathione-rich foods, such as avocados, asparagus, and walnuts, are also good for liver detoxification. The current trend to identify natural products as new cancer preventative agents is based on a conceptual basis and understanding of their mechanisms of action in carcinogenesis.

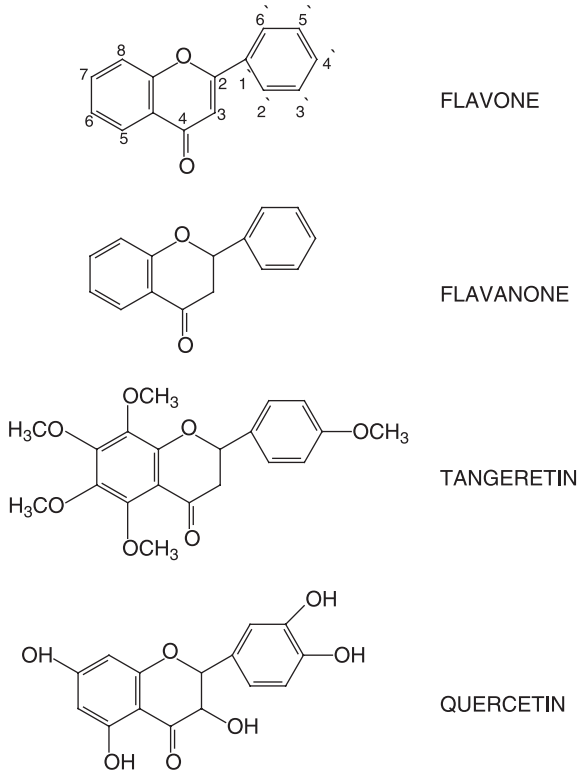

Fig. 2. Chemical structures of flavonoids (Siess et al., 2000).

5.1. Antioxidants

Antioxidants are found in a wide variety fruits and vegetables, plant extracts, beverages, herbs and spices, and semisynthetics (Figs. 2 and 3 and Table 3). They have been found to inhibit various types of cancers (Table 2). One of the most important contributions to cancer is considered to be oxidative damage to DNA. If a cell containing damaged DNA divides before the DNA can be repaired, the result is likely to be a permanent genetic alteration of the steps in carcinogenesis. Body cells that divide rapidly are more susceptible to carcinogenesis because there is less opportunity for DNA repair before cell division (Colic & Pavelic, 2000).

The mechanics for the protective effects of fruits and vegetables and antioxidant nutrients appear to involve the early rather than the later stages of carcinogenesis. There is little doubt that oxidative stress can affect cancer cells in several ways. There is compelling evidence that antioxidants and antiinflammatory compounds (including anti-iron and anti-copper compounds) could be used to modify the redox environment of cancer cells and thus their behavior (Schafer & Buettner, 2001). Additional explanation and support for the concept that tumors contain high numbers of mutated cells, which links this back to the "mutator phenotype" theory, was proposed by Jackson and Loeb (2001). As is consistent with a probable role of oxidative stress in stimulating the mutator phenotype, there is evidence that chronic inflammatory states are linked with elevated cancer risk. It also suggests that antioxidants have the potential to reduce the genetic instability of cancer cells and thus may be useful in treatment. Reddy et al. (2001) demonstrated a mechanism by which antioxidants can also improve the efficacy of chemotherapy. Vitamin C at nontoxic concentrations increased the cytotoxic effects of cisplatin and etoposide against human cervical cancer cells in vitro by stabilizing the p53 protein. However, in other studies (Clement et al., 2001; Halliwell et al., 2000; Palozza et al., 2001), it was shown that antioxidants, including flavonoids and other phenolics, can induce oxidative stress in cancer cells and that some or many of their effects seen in vitro may be due to induction of such stress. β-Carotene at

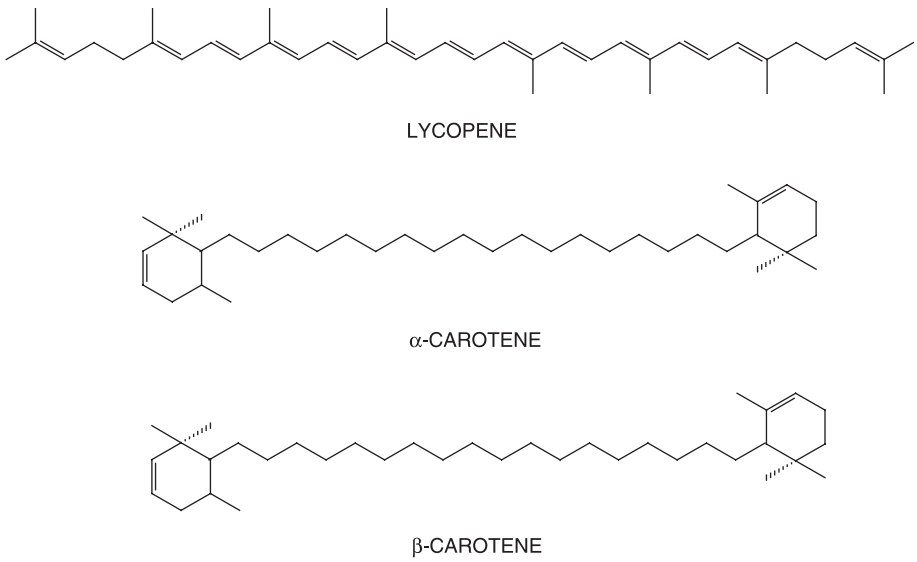

Fig. 3. Chemical structure of lycopene and related carotenoids (α- and β-carotene) (Kim et al., 2000a).

levels just above those seen in human plasma was shown to induce apoptosis in human adenocarcinoma cells in vitro via a free radical-mediated mechanism. Vitamin C was cytotoxic to several cell lines in vitro, again due to free radical generation. These studies highlight the need to consider redox effects when discussing the in vitro actions of antioxidant compounds.

In vitro assessments of potential anticarcinogenesis efficacy include measurements of an agent's antioxidant activity, induction of phase II metabolizing enzymes, and effects upon cellular proliferation and apoptotic control pathways. In vivo efficacy is assessed primarily in rodent models of carcinogenesis that are specific for a given organ target. The role of genetically modified animal models in the in vivo assessment of chemoprevention agents remains unclear. Clinical assessment of the efficacy of a preventive agent comprises a multistep process of identification of an optimal preventive agent (phase 1), demonstration of efficacy in humans through the modulation of reversal of tissue, biochemical, and molecular surrogates for neoplastic transformation and invasion (phase 2), and cancer risk reduction in large cohort trials (phase 3). Opportunities and future needs include the development of reliable, predictive in vivo models of carcinogenesis, careful exploration of the preventive pharmacology of therapeutic agents being used for noncancer prevention indications, and incorporation of genetic risk cohorts to define cancer chemopreventive efficacy.

Vitamin C is known to interfere with the action of nitrites, and further dietary intervention studies are underway to test the ability of ascorbic acid to reverse precancerous lesions of the stomach. Vitamin E is a lipid-phase scavenger of nitrite, oxygen-derived free radicals. However, the evidence linking vitamin E and reduced cancer risks is still inconclusive.

Kakagi et al. (2001) found that with adequate intake of antioxidants during fish oil therapy chemoradiation-induced immunosuppression in humans (1.8 g/day parenteral) can be normalized. Moderate doses of dietary fish oil (4% of diet) increased the efficacy of cisplatin against lung cancer cells in mice. Fish oil and cisplatin were more effective than a combination of fish oil, cisplatin, and vitamins C and E, suggesting that oxidation of the fatty acids improved cell kill (which is to be expected). However, even with the antioxidants, the combination was more effective than cisplatin alone (with soybean oil), demonstrating again that fish oil works by multiple mechanisms and does not require an oxidative action to affect tumor growth (Yam et al., 2001). Similar evidence has also been found by Hardman et al. (2001) in mice fed with fish oil (doses 3% of diet). There was an increase in the efficacy of doxorubicin in mice injected with breast cancer cells (Hardman et al., 2001). In a human study (Aronson et al., 2001), daily oral administration of 10 g of fish oil, along with vitamin E and a healthy, low-fat diet, reduced cyclooxygenase expression in prostatic tissue in 4 of 7 subjects. Since we know from in vitro studies that eicosapentanoic acid reduces cyclooxygenase expression, these are encouraging results, as they suggest that such dietary interventions could reduce cyclooxygenase expression and subsequent inflammation and stimulation of tumour growth.

5.2. Fatty acids

Fatty acids also play an important role in tumor growth, tumor inhibition, and cachexia. Hughes-Fulford et al. (2001) found that cancer cells tend to be unresponsive to normal cholesterol feedback, resulting in overexpression of the low-density lipoprotein receptor. In turn, this allows excessive uptake of low-density lipoprotein, the major carrier of physiological arachidonic acid. Once in the cancer cell, arachidonic acid acts as a substrate for the production of various procancer prostaglandins and leukotrienes that stimulate proliferation and progression. Uptake of ω-3 fatty acids does not have this stimulating effect. Sauer et al. (2000) reported that eicosapentanoic acid inhibits fatty acid uptake and its release in cancer cells and appears to act through a putative ω-3 fatty acid receptor. The inhibitory effect of melatonin on fatty acid uptake is also mediated though its cell surface receptor.

Currier and Miller (2001) reported that both melatonin ($\sim$0.57 mg/kg) and *Echinacea* extract given in the diet improved the survival rate of mice injected with leukemia cells. Melatonin given intraperitoneally to mice (4 mg/kg) reduced the growth of a transplanted prostate cancer and a transformed trophoblast cell line (Shiu et al., 2000; Xi et al., 2001).

5.3. Amino acids and related compounds

Amino acids and other compounds normally found in the blood act in concert as a sort of passive defense system against the development of tumors. According to Kulcsar (1995, 1997a,b), cancer cells are harmed by these compounds because their uptake is unregulated, while normal cells, which carefully regulate their uptake of nutrients, are not adversely affected. One of the things that is interesting in relation to natural compounds in cancer therapy is that Kulcsar (2000) indicated that as many as 13 compounds found in the blood act synergistically to inhibit cancer cell growth in vitro and in animals. Liu et al. (2000) presented evidence that orally administered glutamine inhibits tumor growth in animals. In this case, administration of 300 mg/kg reduced the growth of liver cancer cells injected into mice. The equivalent human dose is $\sim$2.9 g/day. Further evidence for the role of glutamine was provided in a randomized human study by Daniele et al. (2001) who found that oral glutamine reduced intestinal damage caused by chemotherapy. Seventy colorectal cancer patients who had not yet received chemotherapy were randomized to receive glutamine (18 g/day) or placebo. During treatment with chemotherapy

(5-FU and folinic acid), indexes of intestinal permeability and absorption were improved in the group receiving glutamine. In addition, the incidence of diarrhea was reduced in the glutamine group.

Obrador et al. (2001) and Carretero et al. (2000) showed that glutamine administration to tumor-bearing mice decreases mitochondrial glutathione concentrations in cancer cells, leading to increased susceptibility to free radical damage by tumour necrosis factor. Glutamine appeared to act by inhibiting glutathione transport from the cytosol into the mitochondria. Normal cells were not affected. Thus, the result of glutathione administration is increased susceptibility of cancer cells to oxidative stress. Note that this treatment does not increase oxidative stress per se, it only makes cancer cells more susceptible. Furthermore, the locale of the action appears to be the mitochondria, not the nucleus. This suggests the possibility of using oxidative stress as a treatment modality without increasing oxidative damage to DNA; increasing reactive oxygen species within the nucleus could, in theory, increase the mutation rate in cells that are not destroyed.

Whey protein concentrate has also been found to produce anticancer effects in humans with prostate cancer (Bounous, 2000).

5.4. Flavonoids

Flavonoids are the water-soluble pigments in vegetables, fruits, grains, flowers, leaves, and bark. These pigments can scavenge superoxide, hydroxy, and proxyradicals, breaking lipid peroxide chain reactions. They have also been shown to protect cells from X-ray damage, to block progression of cell cycle, to inhibit mutations, to block prostaglandin synthesis, and to prevent multistage carcinogenesis in experimental animals (Abdulla & Gruber, 2000).

The chemical structures of the four common flavonoids are illustrated in Fig. 3. According to Asea et al. (2001), quercetin (found in onions) given intraperitoneally at 150 mg/kg/day reduced the growth of 2 different types of human prostate cancer cells injected into mice. Isoflavones, phenolic acids, and genistein (found in soybeans) were found to inhibit Jurkat T-leukemia cells and bladder cancer (Polkowski & Mazurek, 2000; Siess et al., 2000; Spinozzi et al., 1994; Theodorescu et al., 1998).

Nakagawa et al. (2000) demonstrated that genistein acts synergistically with eicosapentanoic acid in inhibiting the proliferation of human breast cancer cells in vitro. In this study, genistein was reported to inhibit proliferation of pancreatic cancer cells in vitro by a novel mechanism, modulation of DNA synthesis by alteration of glucose oxidation. This action needs to be further studied, but it represents yet another means by which genistein could inhibit tumor growth.

The absorption and metabolism of quercetin (and other phenolics) is still poorly understood. For many years, it was believed that quercetin, curcumin, and some other phenolics were not absorbed at all, since no unchanged compound could be measured in the plasma after oral administration. In the last few years, it has become clear that these phenolics are indeed absorbed but heavily metabolized prior to reaching the plasma. Most of the metabolism is in the form of glucuronidation or the formation of glucuronide conjugates. However, the studies of Drewa et al. (2001) showed the surprising result that quercetin given intraperitoneally to mice at 2–20 mg/kg/day increased the growth of injected melanoma cells. It is not clear why this effect would be seen, and since it suggests that quercetin could increase tumor growth, caution has to be exercised.

Furthermore, the studies of Allred et al. (2001) reported that oral administration of relatively low doses of genistein ($\sim$18 and 36 mg/kg) enhanced the growth of human breast cancer cells injected into mice. The mice had their ovaries removed to simulate estrogenic conditions of postmenopausal women. This study does lend support for avoiding genistein use in the treatment of estrogen-responsive tumors.

In this 6-week study on rats with transplanted human prostate cancer cells, oral administration of curcumin ($\sim$1.5 g/kg) markedly inhibited tumor volume. Moreover, microvessel density (a measure of angiogenesis) was decreased and apoptosis was increased in the tumor tissue. Curcumin was effective when administration was started either at the time of tumor implantation or after establishment of solid tumors. This dose is quite high; the human equivalent is $\sim$24 g/day (Dorai et al., 2001). Orally administered curcumin ($\sim$240 and 1200 mg/kg) also reduced the development of tumors after topical application of a carcinogen in mice (Limtrakul et al., 2001). In this study, it was also shown that curcumin also reduced the expression of *ras* and *fos* oncogenes in the skin. The equivalent human doses are $\sim$2.3 and 11 g/day.

5.5. Resveratrol

Kimura and Okuda (2000) showed that oral administration to mice of resveratrol glycosides (as found naturally in plants) for 32 consecutive days markedly reduced the growth of implanted lung cancer cells and reduced metastasis. Further studies (Kimura & Okuda, 2001) showed that intraperitoneal administration of 2.5 and 10 mg/kg/day inhibited tumor growth, metastasis, and tumor angiogenesis of implanted lung cancer cells in mice. Brakenhielm et al. (2001) demonstrated that oral administration of resveratrol to mice in drinking water reduced the growth of injected fibrosarcoma cells, apparently by inhibiting angiogenesis.

In vitro studies of Igura et al. (2001) added to the literature on the mechanisms of cancer inhibition by resveratrol. Both resveratrol and quercetin inhibit aspects of angiogenesis (proliferation, migration, and tube formation of endothelial cells) at IC_{50} between 15 and 37 μM. Quercetin did not inhibit tube formation. Kozuki et al. (2001) showed that resveratrol suppresses the invasion of

liver cancer cells at 25 μM, which was well below the cytotoxic concentration. Importantly, sera from rats given oral resveratrol also inhibited invasion in vitro. Nielsen et al. (2000) reported that resveratrol at 50 μM improved gap junction intercellular communication in liver cells exposed to carcinogens. Lastly, Ahmad et al. (2001) and Wolter et al. (2001) demonstrated that resveratrol ($\geq$25 μM) inhibited proliferation of colon and epidermoid cancer cells. In both studies, inhibition appeared to be correlated to down-regulation of cyclin-dependent kinases.

5.6. Alkaloids

Lately, it has been found that the naturally occurring bisbenzylisoalkaloids (BBI) can reverse multidrug resistance by increasing the intracellular drug accumulation through inhibiting the activity of P-glycoprotein (Fu et al., 2001). The BBI also show low cytotoxicity on tumor cells. This could solve the problem conventional cancer chemotherapy has with multidrug resistance, which has been linked to overexpression of a membrane associated with P-glycoprotein that acts as an energy-dependent drug efflux pump.

5.7. Semisynthetic anticancer drugs

Most of the current cancer drugs are synthesized against the backbone of one or another natural product (Table 5). Anticancer drugs, such as paclitaxel and docetaxel, arise from the taxol extracts of the English yew tree, *Taxus* spp. (Fan, 1999), and are used to treat refractory ovarian, breast, and other cancers. The inactive extracts of various plants are chemically converted into drugs that affect cells at the molecular level, thereby reversing or inhibiting tumorigenesis. Paclitaxel, for example, promotes tubulin assembly and inhibits cell proliferation. Doxorubicin (from *Streptomyces peucetius*) damages DNA by intercalation of the anthracyclin portion and causes metal ion chelation (Perry, 1992). Camptothecin (from *Camptotheca acuminata*) inhibits the action of topoisomerase I, resulting in cell death. Another prominent molecule is podophyllotoxin, which has been synthetically modified into etoposide and is used to treat lung and testes cancer. Other important molecules include vincristine, vinblastine, colchicine, ellipticine, flavopiridol (a chromone alkaloid from *Rohitukine*), and a pyridoindole alkaloid (from *Ochrosia* spp.) (Mukherjee et al., 2001).

6. Summary

The top two causes of cancer are related to dietary habits and tobacco smoke, and as such, it is largely a preventable disease. The incidence of cancer can thus be substantially reduced by diet modification. Diets rich in vegetables, fruits, and legumes contain large quantities of antioxidants that protect against the deleterious action of free radicals that may lead to cancer development. Consumption of reduced amounts of red meats, saturated fat, salt, and sugar and the avoidance of tobacco smoke and excess consumption of alcohol are other diet modifications that have a positive effect in the prevention of cancer.

It has been shown that whereas synthetic cancer drugs cause nonspecific killing of cells, natural products offer protective and therapeutic actions to all cells with low cytotoxicity and are beneficial in producing nutrient repletion to compromised people. A probing study into the molecular program of apoptosis by cancer chemopreventive agents indicates that the differential effects of studied compounds on distinct molecular pathways of apoptosis warrants further investigation in the effort to utilise the molecular elements of apoptosis in proper cancer chemo-

Table 5
Semisynthetic chemoprotective products commonly used as cancer drugs

Source	Inactive component/active (semisynthetic) component	Mechanism of action	Cancer inhibited (reference)
Taxus baccata	10-Deacetyl baccatin 111: Docetaxel	Promotes tubulin assembly and inhibition of microtubule depolymerization; also acts as a mitotic spindle poison and induces mitotic block in proliferative cells	Breast, ovarian, nonsmall cell lung, head and neck, colorectal, melanoma (Aapro, 1998; Sjostrom et al., 1999)
Taxus brevifolia	Diterpenoid, paclitaxel/taxol	Promotes assembly of microtubules, stabilizes them against depolymerization, and inhibits cell replication; causes apoptosis	Advanced breast, ovarian, adenocarcinoma, and other solid tumors (Fan, 1999; Huang & Fan, 2002; Johnson & Fan, 2002; Johnson et al., 1997)
Streptomyces peucetius	Daunorubicin, doxorubicin	Damages DNA by intercalation of anthracyclin portion, metal ion chelation, generation of free radicals, inhibits DNA topoisomerase 11	Leukemia, breast, Hodgkin's, non-Hodgkin's, lung, small cell, ovarian cancer and sarcomas (Perry, 1992; Zeng et al., 2000)
Rohitukine (Indian plant)	Flavopiridol	CDK modulator	Various cancers (Malumbres & Barbacid, 2001; Mukherjee et al., 2001)
Camptotheca acuminata	10-Hydroxy camptothecin, irinotecan (CPT-11), SN-38	Inhibits action of topoisomerase I, prevents religation of DNA strand, results in cell death	Liver, colorectal, head and neck cancer, leukemia (Chabot, 1997; Friedman et al., 1999; Jiang et al., 2000; Zhang et al., 1998)

prevention and to find biochemical targets for apoptosis-related surrogate end point biomarker assays of chemoprevention.

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References

Aapro, M. (1998). Docetaxel versus doxorubicin in patients with metastatic breast cancer who have failed alkylating chemotherapy: a preliminary report of the randomized phase III trial. 303 Study Group. *Semin Oncol 25*, 7–11.

Abdulla, M., & Gruber, P. (2000). Role of diet modification in cancer prevention. *Biofactors 12*, 45–51.

Adwankar, M. K., & Chitnis, M. P. (1982). In vivo anti-cancer activity of RC-18: a plant isolate from *Rubia cordifolia*, Linn. against a spectrum of experimental tumour models. *Chemotherapy 28*, 291–293.

Agarwal, C., Sharma, Y., & Agarwal, R. (2000). Anticarcinogenic effect of a polyphenolic fraction isolated in human prostrate carcinoma DU145 cells: modulation of cell cycle regulators and induction of G1 arrest. *Mol Carcinog 28*, 129–138.

Ahmad, N., Feyes, D. K., Nieminen, A. L., Agarwal, R., & Mukhtar, H. (1997). Green tea constituent epigallocatechin-3-gallet and induction of apoptosis and cell cycle arrest in human carcinoma cells. *J Natl Cancer Inst 89*, 1881–1886.

Ahmad, N., Adhami, V. M., Afaq, F., Feyes, D. K., & Mukhtar, H. (2001). Resveratrol causes WAF-1/p21-mediated G_1-phase arrest of cell cycle and induction of apoptosis in human epidermoid carcinoma A431 cells. *Clin Cancer Res 7*, 1466–1473.

Allred, C. D., Allred, K. F., Ju, Y. H., Virant, S. M., & Helferich, W. G. (2001). Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose-dependent manner. *Cancer Res 61*, 5045–5050.

Aronson, W. J., Glaspy, J. A., Reddy, S. T., Reese, D., Heber, D., & Bagga, D. (2001). Modulation of omega-3/omega-6 polyunsaturated ratios with dietary fish oils in men with prostate cancer. *Urology 58*, 283–288.

Asea, A., Ara, G., Teicher, B. A., Stevenson, M. A., & Calderwood, S. K. (2001). Effects of the flavonoid drug quercetin on the response of human prostate tumours to hyperthermia in vitro and in vivo. *Int J Hypertherm 17*, 347–356.

Barch, D. H., Rundhaungen, L. M., Stoner, G. D., Pillay, N. S., & Rosche, W. A. (1996). Structure function relationship of the dietary anticarcinogen ellagic acid. *Carcinogenesis 17*, 265–269.

Bounous, G. (2000). Whey protein concentrate (WPC) and glutathione modulation in cancer treatment. *Anticancer Res 20*, 4785–4792.

Bounthnah, C., Bergmann, C., Beck, J. P., Haag-Berrurierm, M., & Anton, R. (1981). Valepotriates, a new class of cytotoxic and antitumor agents. *Planta Med 41*, 21–28.

Brakenhielm, E., Cao, R., & Cao, Y. (2001). Suppression of angiogenesis, tumor growth, and wound healing by resveratrol, a natural compound in red wine and grapes. *FASEB J 15*, 1798–1800.

Brockman, H. E., Stack, H. F., & Waters, M. D. (1992). Antimutagenicity profiles of some natural substances. *Mutat Res 267*, 157–172.

Cardador-Martinez, A., Casttano-Tostado, E., & Loarea-Pina, G. (2002). Antimutagenic activity of natural phenolic compounds present the common bean (*Phaseolus vulgaris*) against aflatoxin B1. *Food Addit Contam 19*, 62–69.

Carretero, J., Obrador, E., Pellicer, J. A., Puscuar, A., & Estrela, J. M. (2000). Mitochondrial glutathione depletion by glutamine in growing tumor cells. *Free Radic Biol Med 29*, 913–923.

Ceruti, A., Ceruti, M., & Vigolo, G. (1986). Natural antitumor compounds of vegetable origin. *G Batteriol Virol Immunol 79*, 187–98 (Italian).

Chabot, G. G. (1997). Clinical pharmacokinetics of irinotecan. *Clin Pharmacokinet 33*, 245–259.

Chapekar, M. S., & Sahasrabudhe, M. B. (1981). Mode of action of GCE: an active anticancer principle isolated from an indigenous plant *Gymnosporia rothiana* laws. *Indian J Exp Biol 19*, 333–336.

Cheng, Y. H., Shen, T. F., Pang, V. F., & Chen, B. J. (1999). Effects of aflatoxin and carotenoids on growth performance and immune response in mule ducklings. *Comp Biochem Physiol Toxicol Pharmacol 128*, 19–26.

Clement, M. V., Ramalingam, J., Long, L. H., & Halliwell, B. (2001). The in vitro cytotoxicity of ascorbate depends on the culture medium used to perform the assay and involves hydrogen peroxide. *Antioxid Redox Signal 3*, 157–163.

Colic, M., & Pavelic, K. (2000). Molecular mechanisms of anticancer activity of natural dietetic products. *J Mol Med 78*, 333–336.

Currier, N. L., & Miller, S. C. (2001). *Echinacea purpurea* and melatonin augment natural-killer cells in leukemic mice and prolong life span. *J Altern Complement Med 7*, 241–251.

Daniele, B., Perrone, F., Gallo, C., Pignata, S., De Marintino, S., Devive, R., Barletta, E., Tambaro, R., Abbiati, R., & D'Agostono, L. (2001). Oral glutamine in the prevention of fluorouracil induced intestinal toxicity: a double blind, placebo controlled, randomised trial. *Gut 48*, 28–33.

Day, A. J., Bao, Y., Morgan, M. R., & Williamson, G. (2000). Conjugation position of quercetin glucuronides and effect on biological activity. *Free Radic Biol Med 29*, 1234–1243.

Demark-Wahnefried, W., Price, D. T., Polascik, T. J., Robertson, C. N., Anderson, E. E., Paulson, D. F., Walther, P. J., Gannon, M., & Vollmer, R. T. (2001). Pilot study of dietary fat restriction and flaxseed supplementation in men with prostate cancer before surgery: exploring the effects on hormonal levels, prostate-specific antigen, and histopathologic features. *Urology 58*, 47–52.

Doll, R., & Peto, R. (1981). The cause of cancer. Quantitative estimates of available risks of cancer in the United States today. *J Natl Cancer Inst 66*, 1192–1308.

Dong, Y., Yang, M. M., & Kwan, C. Y. (1997). In vitro inhibition of proliferation of HL-60 cells by tetrandrine and *Coriolus versicolor* peptide derived from Chinese medicinal herbs. *Life Sci 60*, 135–140.

Dorai, T., Cao, Y. C., Dorai, B., Buttyan, R., & Katz, A. E. (2001). Therapeutic potential of curcumin in human prostate cancer: III. Curcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells in vivo. *Prostate 47*, 293–303.

Drewa, G., Wozqak, A., Palgan, K., Schachtschsbel, D. O., Grzanka, A., & Sujikowska, R. (2001). Influence of quercetin on B16 melanotic melanoma growth in C57BL/6 mice and on activity of some acid hydrolases in melanoma tissue. *Neoplasma 48*, 12–18.

Duong Van Huyen, J. P., Sooryanarayana, V., Delignat, S., Bloch, M. F., Kazatchkine, M. D., & Kaveri, S. V. (2001). Variable sensitivity of lymphoblastoid cells to apoptosis induced by *Viscum album* Qu FrF, a therapeutic preparation of mistletoe lectin. *Chemotherapy 47*, 366–376.

Eberhardt, M. V., Lee, C. Y., & Lui, R. H. (2000). Antioxidant activity of fresh apples. *Nature 405*, 903–904.

Fan, W. (1999). Possible mechanisms of Paclitaxel-induced apoptosis. *Biochem Pharmacol 57*, 1215–1221.

Friedman, H. S., Petros, W. P., Friedman, A. H., Schaaf, L. J., Kerby, T., Lawyer, J., Parry, M., Houghton, P. J., Lovell, S., Rasheed, K., Cloughsey, T., Stewart, E. S., Colvin, O. M., Provenzale, J. M., McLendon, R. E., Bigner, D. D., Cokgor, I., Haglund, M., Rich, J., Ashley, D., Malczyn, J., Elfring, G. L., & Miller, L. L. (1999). Irinotecan therapy in adults with recurrent or progressive malignant glioma. *J Clin Oncol 17*, 1516–1525.

Fu, L. W., Deng, Z. A., Pan, Q. C., & Fan, W. (2001). Screening and

discovery of novel MDR modifiers from naturally occurring bisbenzylisoquinoline alkaloids. *Anticancer Res 21*, 2273–2280.

Furusawa, E., & Furusawa, S. (1985). Anticancer activity of a natural product, viva-*natural*, extracted from *Undaria pinnantifida*. *Oncology 42*, 364–369.

Galvano, F., Piva, A., Ritieni, A., & Galvano, G. (2001). Dietary strategies to counteract the effects of mycotoxins: a review. *J Food Prot 64*, 120–131.

Giovannucci, E. (1999). Tomatoes, tomato based products, lycopene and cancer: review of the epidemiological literature. *J Natl Cancer Inst 91*, 317–331.

Gogate, S. S. (1991). Cytotoxicity of neem leaf extract: an antitumor. *Natl Med J India 9*, 297.

Halliwell, B., Clement, M. V., Ramalingam, J., & Long, L. H. (2000). Hydrogen peroxide. Ubiquitous in cell culture and in vivo? *IUBMB Life 50*, 251–257.

Handelman, G. J. (2001). The evolving role of carotenoids in human biochemistry. *Nutrition 17*, 818–822.

Hardman, W. E., Avula, C. P., Fernandes, G., & Cameron, I. L. (2001). Three percent dietary fish oil concentrate increased efficacy of doxorubicin against mda-mb 231 breast cancer xenografts. *Clin Cancer Res 7*, 2041–2049.

Hecht, S. S., Kenney, P. M., Wang, M., Trushin, N., Agarwal, S., Rao, A. V., & Upadhyaya, P. (1999). Evaluation of butylated hydroxyanisole, *myo*-inositol, curcumin, esculetin, resveratrol, and lycopene as inhibitors of benzo[*a*]pyrene plus 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in A/J mice. *Cancer Lett 137*, 123–130.

Hirano, T., Oka, K., Mimaki, Y., Kuroda, M., & Sashida, Y. (1996). Potent growth inhibitory activity of a novel *Ornithogalum* cholestane glycoside on human cells: induction of apoptosis in promyelocytic leukemia HL-60 cells. *Cancer Lett 58*, 789–798.

Huang, Y., & Fan, W. (2002). IκB kinase activation is involved in regulation of paclitaxel-induced apoptosis in human tumour cell lines. *Mol Pharmacol 61*, 105–113.

Hughes-Fulford, M., Chen, Y., & Tjandrawinata, R. R. (2001). Fatty acid regulates gene expression and growth of human prostate cancer PC-3 cells. *Carcinogenesis 22*, 701–707.

Igura, K., Ohta, T., Kuroda, Y., & Kaji, K. (2001). Resveratrol and quercetin inhibit angiogenesis in vitro. *Cancer Lett 171*, 11–16.

Jackson, A. L., & Loeb, L. A. (2001). The contribution of endogenous sources of DNA damage to the multiple mutations in cancer. *Mutat Res 477*, 7–21.

Jiang, J. F., Lui, W. J., & Ding, J. (2000). Regulation of telomerase activity in camptothecin induced apoptosis of leukemia HL-60 cells. *Acta Pharmacol Sin 21*, 759–764.

Jing, Y., Ohizumi, H., Kawazoe, N., Hashimoto, S., Masuda, Y., Nakajo, S., Yoshida, T., Kuroiwa, Y., & Nakaya, K. (1994). Selective inhibitory effect of bufalin on growth of human tumour cells in vitro: association with the induction of apoptosis in leukemia HL-60 cells. *Jpn J Cancer Res 85*, 645–651.

Johnson, K. R., & Fan, W. (2002). Reduced expression of p53 and $p21^{WAF1/CIP1}$ sensitizes human breast cancer cells to paclitaxel and its combination with 5-fluorouracil. *Anticancer Res 22*, 1–8.

Johnson, K. R., Wang, L., Miller, M. C., Willingham, M. C., & Fan, W. (1997). 5-Fluorouracil interferes with paclitaxel cytotoxicity against human solid tumour cells. *Clin Cancer Res 3*, 1739–1745.

Kakagi, K., Yamamori, H., & Furukawa, K. (2001). Perioperative supplementation of EPA reduces immunosuppression induced by postoperative chemoradiation therapy in patients with esophageal cancer. *Nutrition 17*, 478–479.

Kim, D. J., Takasuka, N., Nishino, H., & Tsuda, H. (2000a). Chemoprotection of lung cancer by lycopene. *BioFactors 13*, 95–102.

Kim, M. S., So, H. S., Lee, K. M., Park, J. S., Lee, J. H., Moon, S. K., Ryu, D. G., Jung, B. H., Kim, Y. K., Moon, G., & Park, R. (2000b). Activation of caspase cascades in Korean mistletoe (*Viscum* var. *coloratum*) lectin-II-induced apoptosis of human myelo U937 cells. *Gen Pharmacol 34*, 349–355.

Kimura, Y., & Okuda, H. (2000). Effects of naturally occurring stilbene glucosides from medicinal plants and wine, on tumour growth and lung metastasis in Lewis lung carcinoma-bearing mice. *J Pharm Pharmacol 52*, 1287–1295.

Kimura, Y., & Okuda, H. (2001). Resveratrol isolated from *Polygonum cuspidatum* root prevents tumor growth and metastasis to lung and tumor-induced neovascularization in Lewis lung carcinoma-bearing mice. *J Nutr 131*, 1844–1849.

King, T. J., Khachlik, F., Bortkiewicz, H., Fukushima, L. H., Scott, M., & Bertram, J. S. (1997). Metabolites of dietary carotenoids as potential cancer preventative agents. *Pure Appl Chem 69*, 2135–2140.

Klein, E. A., Thompson, I. M., Lippman, S. M., Goodman, P. J., Albanes, D., Taylor, P. R., & Coltman, C. (2001). SELECT: the next prostrate cancer prevention trial. Selenium and vitamin E cancer prevention trial. *J Urol 166*, 1311–1315.

Kozuki, Y., Miura, Y., & Yagasaki, K. (2001). Resveratrol suppresses hepatoma cell invasion independently of its anti-proliferative action. *Cancer Lett 167*, 151–156.

Kulcsar, G. (1995). Inhibition of the growth of a murine and various human tumor cell lines in culture and in mice by mixture of certain substances of the circulatory system. *Cancer Biother 10*, 157–176.

Kulcsar, G. (1997a). Apoptosis of tumor cells induced by substances of the circulatory system. *Cancer Biother Radiopharm 12*, 19–26.

Kulcsar, G. (1997b). Theoretical and literary evidence for the existence of the passive antitumor defence system. *Cancer Biother Radiopharm 12*, 281–286.

Kulcsar, G. (2000). Synergistic potentiating effect of D(+)-mannose, orotic, and hippuric acid sodium salt on selective toxicity of a mixture of 13 substances of the circulatory system in culture for various tumor cell lines. *Cancer Detect Prev 24*, 485–495.

Kuo, C. L., Chou, C. C., & Yung, B. Y. (1995). Berberine complexes with DNA in the berberine-induced apoptosis in human leukemic HL-60 cells. *Cancer Lett 93*, 193–200.

Langset, L. (1995). *Oxidants, Antioxidants and Disease Prevention. ILSI Europe Concise Monograph Series*. Brussels: ILSI Europe/ILSI Press.

Li, J. K., & Lin-Shia, S. Y. (2001). Mechanisms of cancer chemoprevention by curcumin. *Proc Natl Sci Counc Repub China Part B 25*, 59–66.

Limtrakul, P., Anuchapreeda, S., Lipigorngoson, S., & Dunn, F. W. (2001). Inhibition of carcinogen induced c-Ha-*ras* and c-*fos* proto-oncogenes expression by dietary curcumin. *BMC Cancer 1*, 1.

Lin, C. C., & Huang, P. C. (2000). Antioxidant and hepatoprotective effects of *Acanthopanax*. *Phytother Res 14*, 489–494.

Liu, S. L., Shi, D. Y., Shen, Z. H., & Wu, Y. D. (2000). Effects of glutamine on tumor growth and apoptosis of hepatoma cells. *Acta Pharmacol Sin 21*, 668–672.

Lyu, S. Y., Park, W. B., Choi, K. H., & Kim, W. H. (2001). Involving of caspase-3 in apoptosis induced by *Viscum album* agglutinin in HL-60 cells. *Biosci Biotechnol Biochem 65*, 534–541.

Malumbres, M., & Barbacid, M. (2001). Milestones in cell division: to cycle or not to cycle: a critical decision in cancer. *Nat Rev Cancer 1*, 222–231.

Mann, J. (2002). Natural products in cancer chemotherapy: past, present and future. *Nat Rev Cancer 2*, 143–148.

Marnewick, J. L., Gelderblom, W. C. A., & Joubert, E. (2000). An investigation on the antimutagenic properties of South African herbal teas. *Mutat Res 471*, 157–166.

Michaud, D. S., Fesknich, D., Rimm, E. B., Colditz, G. A., Speizer, F. E., Willett, W. C., & Giovannucci, E. (2000). Intake of specific carotenoids and risk of lung cancer in 2 prospective US cohorts. *Am J Clin Nutr 72*, 990–997.

Mukherjee, A. K., Basu, S., Sarkar, N., & Ghosh, A. C. (2001). Advances in cancer therapy with plant based natural products. *Curr Med Chem 8*, 1467–1486.

Nakagawa, H., Yamamoto, D., Kiyozuka, Y., Tsuta, K., Uemura, Y., Hioki, K., Tsutsui, Y., & Tsubura, A. (2000). Effects of genistein and synergistic action in combination with eicosapentaenoic acid on the growth of breast cancer cell lines. *J Cancer Res Clin Oncol 126*, 448–454.

Nakahata, N., Kutsuwa, M., Kyo, R., Kubo, M., Hayashi, K., & Ohizumi, Y. (1998). Analysis of inhibitory effects of *Scutellariae radix* and baicalein on prostaglandin E2 production in rat C6 glioma cells. *Am J Clin Med 26*, 311–323.

Nielsen, M., Ruch, R. J., & Vang, O. (2000). Resveratrol reverses tumor-promoter-induced inhibition of gap-junctional intercellular communication. *Biochem Biophys Res Commun 275*, 804–809.

Nishino, H., Tokuda, H., Murakoshi, M., Satomi, Y., Masuda, M., Onozuka, M., Yamaguchi, S., Tsuruta, J., Okuda, M., Khachik, F., Narisawa, T., Takasuka, N., & Yano, M. (2000). Cancer prevention by natural carotenoids. *BioFactors 13*, 89–94.

Obrador, E., Carretero, J., Esteve, J. M., Peller, J. A., Petschen, I., & Estrela, J. M. (2001). Glutamine potentiates TNF-α-induced tumor cytotoxicity. *Free Radic Biol Med 31*, 642–650.

O'Keefe, S. J., Kidd, M., Espitalier-Noel, G., & Owira, P. (1999). Don't thank fiber; blame meat and milk. *Am J Gastroenterol 94*, 1373–1380.

Paiva, S. A., & Russell, R. M. (1999). Beta-carotene and other carotenoids as antioxidants. *J Am Coll Nutr 18*, 426–433.

Palozza, P., Calviello, G., Serini, S., Maggiano, N., Lanza, P., Ranelletti, F. O., & Bartoli, G. M. (2001). Beta-carotene at high concentrations induces apoptosis by enhancing oxy-radical production in human adenocarcinoma cells. *Free Radic Biol Med 30*, 1000–1007.

Park, W. B., Lyu, S. Y., Kim, J. H., Choi, S. H., Chung, H. K., Ahn, S. H., Hong, S. Y., Yoon, T. J., & Choi, M. J. (2001). Inhibition of tumour growth and metastasis by Korean mistletoe lectin is with apoptosis and antiangiogenesis. *Cancer Biother Radiopharm 16*, 439–447.

Perry, M. C. (1992). *The Chemotherapy Sourcebook*. Baltimore: Williams & Wilkins.

Poginsky, B., Westendorf, J., Blomeke, B., Marquardt, H., Hewer, A., Grover, P. L., & Phillips, D. H. (1991). Evaluation of DNA-binding activity of hydroxyanthraquinones occurring in *Rubia tinctorum* L. *Carcinogenesis 12*, 1265–1271.

Polkowski, K., & Mazurek, A. P. (2000). Biological properties of genistein. A review of in vitro and in vivo data. *Acta Pol Pharm 57*, 135–155.

Pryor, W. A., Stahl, W., & Rock, C. L. (2000). Beta carotene: from biochemistry to clinical trials. *Nutr Rev 58*, 39–53.

Rauscher, R., Edenharder, R., & Platt, K. L. (1998). In vitro antimutagenic and in vivo anticlastogenic effects of carotenoids and solvent extracts from fruits and vegetables rich in carotenoids. *Mutat Res 413*, 129–142.

Reddy, V. G., Khanna, N., & Singh, N. (2001). Vitamin C augments chemotherapeutic response of cervical carcinoma HeLa cells by stabilizing p53. *Biochem Biophys Res Commun 282*, 409–415.

Ribereau-Gayon, G., Jung, M. L., Frantz, M., & Anton, R. (1997). Modulation of cytotoxicity and enhancement of cytokine release induce *Viscum album* L. extracts or mistletoe lectins. *Anticancer Drugs 8*, S3–S8.

Sauer, L. A., Dauchy, R. T., & Blask, D. E. (2000). Mechanism for the antitumor and anticachectic effects of $n-3$ fatty acids. *Cancer Res 15*, 5289–5295.

Schafer, F. Q., & Buettner, G. R. (2001). Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple. *Free Radic Biol Med 30*, 1191–1212.

Sheng, Y., Pero, R. W., Amiri, A., & Bryngelsson, C. (1998). Induction of apoptosis and inhibition of proliferation in human tumor cells treated with extracts of *Uncaria tomentosa*. *Anticancer Res 18*, 3363–3368.

Shiu, S. Y., Xi, S. C., Xu, J. N., Mei, L., Pang, S. F., Yao, K. M., & Wong, J. T. (2000). Inhibition of malignant trophoblastic cell proliferation in vitro and in vivo by melatonin. *Life Sci 67*, 2059–2074.

Siess, M. H., Le Bon, A. M., Canivenc-Lavier, M. C., & Suschetet, M. (2000). Mechanisms involved in the chemoprevention of flavonoids. *BioFactors 12*, 193–199.

Sjostrom, J., Blomqvist, C., Mouridsen, H., Pluzanska, A., Ottosson-Lonn, S., Bengtsson, N. O., Ostenstad, B., Mjaaland, I., Palm-Sjovall, M., Wist, E., Valvere, V., Anderson, H., & Bergh, J. (1999). Docetaxel compared with sequential methotrexate and 5-fluorouracil in patients with advanced breast cancer after anthracycline failure: a randomised phase III study with crossover on progression by the Scandinavian Breast Group. *Eur J Cancer 35*, 1194–1201.

Spinozzi, F., Pagliacci, M. C., Migliorati, G., Moraca, R., Grignani, F., Riccardi, C., & Nicoletti, I. (1994). The natural tyrosine kinase inhibitor genistein produces cell cycle arrest and apoptosis in Jurkat T-leukemia cells. *Leuk Res 18*, 431–439.

Stahl, W., Heinrich, U., Jungnann, H., Sies, H., & Tronnier, H. (2000). Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans. *Am J Clin Nutr 71*, 795–798.

Takasaki, M., Konoshima, T., Etoh, H., Pal Singh, I., Tokuda, H., & Nishino, H. (2000). Cancer chemopreventive activity of euglobal-G1 from leaves of *Eucalyptus grandis*. *Cancer Lett 155*, 61–65.

Theodorescu, D., Laderoute, K. R., Calaogan, J. M., & Guilding, K. M. (1998). Inhibition of human bladder cancer cell motility by genistein is dependent on epidermal growth factor receptor but not p21 *ras* gene expression. *Int J Cancer 78*, 775–782.

Timbrell, J. A. (2000). Toxic responses to foreign compounds. In J. A. Timbrell (Ed.), *Principles of Biochemical Toxicology* (3rd ed.) (pp. 272–273). London: Taylor & Francis (Chapter 6).

Wattenberg, L. W., & Estensen, R. D. (1996). Chemopreventive effects of *myo*-inositol and dexamethasone on benzo[*a*]pyrene and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone-induced pulmonary carcinogenesis in female A/J mice. *Cancer Res 56*, 5132–5135.

Watzl, B., Bub, A., Brandstetter, B. R., & Rechkemmer, G. (1999). Modulation of human T-lymphocyte functions by the consumption of carotenoid-rich vegetables. *Int Rev Immunol 18*, 527–546.

Witschi, H., Espiritu, I., & Uyeminami, D. (1999). Chemoprevention of tobacco smoke-induced lung tumours in A/J strain mice with dietary *myo*-inositol and dexamethasone. *Carcinogenesis 20*, 1375–1378.

Wolter, F., Akoglu, B., Clausnitzer, A., & Stein, J. (2001). Downregulation of the cyclin d1/cdk4 complex occurs during resveratrol-induced cell cycle arrest in colon cancer cell lines. *J Nutr 131*, 2197–2203.

Xi, S. C., Siu, S. W., Fong, S. W., & Shiu, S. Y. (2001). Inhibition of androgen-sensitive LNCaP prostate cancer growth in vivo by melatonin: association of antiproliferative action of the pineal hormone with mt1 receptor protein expression. *Prostate 46*, 52–61.

Yam, D., Peled, A., & Shinitzky, M. (2001). Suppression of tumor growth and metastasis by dietary fish oil combined with vitamins E and C and cisplatin. *Cancer Chemother Pharmacol 47*, 34–40.

Yuan, J., Gu, Z. L., Chou, W. H., & Kok, C. Y. (1999). Elemene induces apoptosis and regulates expression of bcl-2 protein in human leukemia K562 cells. *Chung-Kuo Yao Li Hsueh Pao 20*, 103–106.

Zeng, S., Chen, Y. Z., Fu, L., Johnson, K. R., & Fan, W. (2000). In vitro evaluation of schedule-dependent interactions between docetaxel and doxorubicin against human breast and ovarian cancer cells. *Clin Cancer Res 6*, 3766–3773.

Zhang, R., Li, Y., Cai, Q., Liu, T., Sun, H., & Chambless, B. (1998). Preclinical pharmacology of the natural product anticancer agent 10-hydroxycamptothecin, an inhibitor of topoisomerase I. *Cancer Chemother Pharmacol 41*, 257–267.

Zhang, Z., Liong, E. C., Lau, T. Y., Leung, K. M., Fung, P. C., & Tipoe, G. L. (2000). Induction of apoptosis by hexamethyl bisacetamide is p53-dependent with telomerase activity but not with terminal differentiation. *Int J Oncol 16*, 887–892.

Zhao, Y., Cao, J., Ma, H., & Liu, J. (1997). Apoptosis induced by tea polyphenols in HL-60 cells. *Cancer Lett 121*, 163–167.

Zheng, S., Yang, H., Zhang, S., Wang, X., Yu, L., Lu, J., & Li, J. (1997). Initial study on naturally occurring products from traditional Chinese herbs and vegetables for chemoprevention. *J Cell Biochem Suppl 27*, 106–112.