Natural Phenolic Compounds From Medicinal Herbs and Dietary Plants: Potential Use for Cancer Prevention

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INTRODUCTION

Cancer is a growing health problem around the world and is the second leading cause of death after heart disease (1). According to a recent report by the World Health Organization (WHO) (http://www.who.int/cancer/en/), from a total of 58 million deaths worldwide in 2005, cancer accounted for 13%. There are now more than 10 million cases of cancer per year worldwide, including a group of more than 100 diseases such as cancer of the liver, lung, stomach, colon, breast, and so forth (2,3). The most rational way to affect carcinogenesis is by interfering with modulation steps (initiation, promotion, and progression) as well as the associated signal transduction pathways (4). There are numerous physiological and biochemical carcinogens, for example, ultraviolet and ionizing radiation; asbestos and tobacco smoke (5); infections by virus (e.g., hepatitis B virus causing liver cancer and human papilloma virus causing cervical cancer) (6,7); bacteria (Helicobacter pylori causing gastric cancer) (8) and parasites (schistosomiasis causing bladder cancer) (9); and contamination of food by mycotoxins (e.g., aflatoxins causing liver cancer) (10). Some kinds of cancer are due to oxygen-centered free radicals and other reactive oxygen species because overproduction of such free radicals can cause oxidative damage to biomolecules (e.g., lipids, proteins, DNA) (11).

There are no extremely effective drugs to treat most cancers. There is a general call for new drugs that are highly effective, possess low toxicity, and have a minor environment impact. Novel natural products offer opportunities for innovation in drug discovery (12). In fact, natural products play a major role in cancer prevention and treatment. A considerable number of antitumor agents currently used in the clinic are of natural origin. For instance, over half of all anticancer prescription drugs approved internationally between the 1940s and 2006 were natural products or their derivatives (13). Among them, plants have been the chief source of natural compounds used for medicine. During the 1960s, the National Cancer Institute (United States) began to screen plant extracts with antitumor activity (14). Natural compounds isolated from medicinal plants, as rich sources of novel anticancer drugs, have been of increasing interest since then. Traditional medicinal herbs have been used for pharmaceutical and dietary therapy for several millennia in East Asia, for example, in China, Japan, India, Thailand, and are currently widely used in cancer therapy (12). During long-term folk practice, a large number of anticancer medicinal herbs and many relevant prescriptions have been screened and used for treating and preventing various cancers (15). Recently, many studies have reported medicinal plants in treatment and prevention of cancer (13).

Earlier investigation showed that an average of 35% of overall human cancer-related mortality was attributed to diet (16). Substantial evidence from population as well as laboratory studies have revealed an inverse relationship between sufficient consumption of fruit and vegetables and the risk of specific cancers,
that is, a high dietary intake of fruits and vegetables as well as whole grains is strongly associated with reduced risk of cancer (2). Many clinical trials on the use of nutritional supplements and modified diets to prevent cancer are ongoing (17). Dietary plant—such as fruits, vegetables, spices, cereals, and edible tubers/roots—which also contain significant levels of bioactive natural compounds, may provide human health benefits beyond basic nutrition to reduce the risk of many chronic diseases including cancer (18). The cancerprotective effects elicited by these dietary compounds are believed to be due to the induction of cellular defense systems including the detoxifying and antioxidant enzymes system as well as the inhibition of anti-inflammatory and anticell growth signaling pathways culminating in cell cycle arrest and/or cell-death (19).

Phytochemicals are defined as bioactive nonessential nutrients from plants (phyto is derived from the Greek word phyto, which means plant). They have a variety of human health effects such as possessing putative chemo-reventive properties (anticarcinogenic and antimitagentic) and interfering with tumor promotion and progression (2,19). The National Cancer Institute, based on numerous reports describing anticancer activity, identified about 40 edible plants possessing cancer-preventive properties (20). Moreover, there are more than 400 species of traditional Chinese medicinal herbs associated with anticancer (12). It is estimated that more than 5,000 individual phytochemicals have been identified in fruits, vegetables, grains, and other plants, mainly classified as phenolics, carotenoids, vitamins, alkaloids, nitrogen-containing compounds, and organosulfur compounds. Among the great structural diversity of phytochemicals, pheno- lic compounds have attracted considerable interest and the most attention for their wide variety of bioactivities (21).

Phenolic compounds provide essential functions in the reproduction and growth of plants; act as defense mechanisms against pathogens, parasites, and predators; as well as contribute to the color of plants (22). In addition, phenolics abundant in vegetables and fruits are reported to play an important role as chemopreventive agents; for example, the phenolic components of apples have been linked with inhibition of colon cancer in vitro (23). Many phenolic compounds have been reported to possess potent antioxidant activity and to have anticanecer or anticarcinogenic/antimitagentic, antiatherosclerotic, antibacterial, antiviral, and anti-inflammatory activities to a greater or lesser extent (21–24). Our recent studies have characterized a large number of natural phenolic compounds from 112 traditional Chinese medicinal herbs associated with anticancer, 133 traditional Indian medicinal herbs, and about 50 dietary plants (e.g., spices, cereals, vegetables, and fruits) and evaluated their antioxidant activity and other bioactivities (12,25–33). Hundreds of natural phenolic compounds have been identified from our tested medicinal herbs and dietary plants, mainly includ- ing phenolic acids, flavonoids, tannins, stilbenes, curcuminoinds, coumarins, lignans, quinones, and phenolic mixtures and other phynylethanoids and phenylpropanoids. Their physiological and pharmacological functions may originate from their antioxidant and free radical scavenging properties and function of regulat- ing detoxifying enzymes (2). Further, these antioxidant activities are related to the structures of phenolic compounds, generally depending on the number and positions of hydroxyl groups and glycosylation or other substituents (31,34).

### CHEMISTRY AND OCCURRENCE OF PHENOLIC COMPOUNDS FROM MEDICINAL HERBS AND DIETARY PLANTS

Phenolics are compounds possessing one or more aromatic rings bearing one or more hydroxyl groups with over 8,000 structural variants and generally are categorized as phenolic acids and analogs, flavonoids, tannins, stilbenes, curcuminoinds, coumarins, lignans, quinones, and others based on the number of phenolic rings and of the structural elements that link these rings (4).

### Phenolic Acids and Analogs

Phenolic acids are a major class of phenolic compounds, widely occurring in the plant kingdom (12). As shown in Fig. 1, predominant phenolic acids include hydroxybenzoic acids (e.g., gallic acid, p-hydroxybenzoic acid, protocatechuic acid, vanillic acid, and syringic acid) and hydroxycinnamic acids (e.g., fer- ulic acid, caffeic acid, p-coumaric acid, chlorogenic acid, and sinapic acid) (31). Natural phenolic acids, either occurring in the free or conjugated forms, usually appear as esters or amides. Due to their structural similarity, several other polyphenols are considered as phenolic acid analogs such as capsaicin, rosmarinic acid, gingerol, gossypol, parado, tyrosol, hydroxytyrosol, el- lagic acid, cynarin, and salvianolic acid B (4,21) (Fig. 1).

Gallic acid is widely distributed in medicinal herbs, such as *Barringtonia racemosa*, *Cornus officinalis*, *Cassia auriculata*, *Polygonum aviculare*, *Punica granatum*, *Rheum officinale*, *Rhus chinensis*, *Sanguisorba officinalis*, and *Terminalia chebula* as well as dietary spices, for example, thyme and clove (12,28–31). Other hydroxybenzoic acids are also ubiquitous in medicinal herbs and dietary plants (spices, fruits, vegetables). For example, Dolichos biflorus, *Feronia elephantum*, and *Paeonia lactiflora* contain hydroxybenzoic acid; *Cinnamomum cassia*, *Lawsonia inermis*, *dill*, grape, and star anise possess protocatechuic acid; *Foeniculum vulgare*, *Ipomoea turpethum*, and *Picrorhiza scro- phulariflora* have vanillic acid; *Ceratostigma willmottianum* and sugarcane straw possess syringic acid (12,28–31,35,36).

Ferulic, caffeic, and p-coumaric acid are present in many medicinal herbs and dietary spices, fruits, vegetables, and grains (12). Wheat bran is a good source of ferulic acids. Free, soluble-conjugated, and bound ferulic acids in grains are present in the ratio of 0.1:1:100 (37). Red fruits (blueberry, blackberry, chokeberry, strawberry, red raspberry, sweet cherry, sour cherry, elderberry, black currant, and red currant) are rich in hydroxycinnamic acids (caffeic, ferulic, p-coumaric acid) and p-hydroxybenzoic, ellagic acid, which contribute to their anti-oxidant activity (38). Chlorogenic acids are the ester of caffeic
FIG. 1. Chemical structures of common phenolic acids and analogs from medicinal herbs and dietary plants.
acids and are the substrate for enzymatic oxidation leading to browning, particularly in apples and potatoes. We also found that chlorogenic acid is a major phenolic acid from medicinal plants especially in the species of Apocynaceae and Asclepiadaceae (39).

Salvianolic acid B is a major water-soluble polyphenolic acid extracted from Radix salviae miltiorrhizae, which is a common herbal medicine clinically used as an antioxidant agent for thousands of years in China. There are 9 activated phenolic hydroxyl groups that may be responsible for the release of active hydrogen to block lipid peroxidation reaction (3). Rosmarinic acid is an antioxidant phenolic compound, which is found in many dietary spices such as mint, sweet basil, oregano, rosemary, sage, and thyme (28). Gossypol, a polyphenolic aldehyde, derived from the seeds of cotton plant (genus Gossypium, family Malvaceae), has contraceptive activity and can cause hypokalemia in some men (21). Gingerol, a phenolic substance, is responsible for the spicy taste of ginger (2).

Flavonoids

Flavonoids are a group of more than 4,000 phenolic compounds that occur naturally in plants (40). These compounds commonly have the basic skeleton of phenylbenzopyrane structure (C6-C3-C6) consisting of 2 aromatic rings (A and B rings) linked by 3 carbons that are usually in an oxygenated central pyran ring, or C ring (12). According to the saturation level and opening of the central pyran ring, they are categorized mainly into flavones (basic structure, B ring binds to the 2 position), flavonols (having a hydroxyl group at the 3 position), flavanones (dihydroflavones) and flavanones (dihydroflavonols; 2–3 bond is saturated), flavans (flavan-3-ols and flavan-3,4-diols; C-ring is 1-pyran), anthocyanins (anthocyanidins; C-ring is 1-pyran, and 1–2 and 3–4 bonds are unsaturated), chalcones (C-ring is opened), isoflavonoids (mainly isoflavones; B ring binds to the 3 position), neoflavonoids (B ring binds to the 4-position), and biflavonoids (dimer of flavones, flavonols, and flavanones) (12,31,40,41) (main structure groups/subgroups; see Fig. 2). In nature, flavonoids can occur either in the free or conjugated forms, and often in plants they are mainly present as glycosides with a sugar moiety or more sugar moieties linked through an OH group (O-glycosides) or through carbon-carbon bonds (C-glycosides); but some flavonoids are present as aglycones (4,31). More than 80 different sugars have been discovered bound to flavonoids, and common glycosides include glucoside, glucuronide, galactoside, arabinoside, rhamnoside, apiosylglucose, and malonyl (42) (Fig. 2).

Different kinds of flavonoids are present in practically all dietary plants, like fruits and vegetables, and we also found that flavonoids are the largest class of phenolics in the tested medicinal herbs and dietary spices in our previous studies (12,28–33,39). Some common different categories of flavonoids from medicinal herbs and dietary plants are shown in Fig. 3. The most common flavones are luteolin, apigenin, baicalein, chrysin, and their glycosides (e.g., apigenin, vitexin, and baicalin), mainly distributed in the Labiatae, Asteraceae, and so forth, such as roots of Scutellaria baicalensis, inflorescences of Chrysanthemum morifolium, and aerial parts of Artemisia annua. Their major food plant sources are parsley, thyme, cherries, tea, olives, broccoli, and legumes (4,40). Quercetin, kaempferol, myricetin, morin, galangin, and their glycosides (e.g., rutin, quercitrin, and astragalin) are the predominant flavonols. These flavonols have a large range of food sources such as onions, cherries, apples, broccoli, kale, tomato, berries, tea, red wine, caraway, cumin, and buckwheat; and they also occur in many medicinal herbs associated with anticancer, for example, flowers of Sophora japonica and Rosa chinensis, aerial parts of A. annua, rhizomes of Alpinia officinarum, and fruits (hawthorn) of Crataegus pinnatifida (12,28). Among these common flavonols, quercetin is one of the major dietary flavonoids, found in a broad range of fruit, vegetables, and beverages with a daily intake in Western countries of 25–30 mg (3). Flavanones such as naringenin, hesperetin, eriodictyol, and their glycosides (e.g., naringin, hesperidin, and liquiritin) and flavanones (taxifolin) are mainly found in citrus fruits (e.g., oranges, lemons, and aurantium), grape, and the medicinal herbs of Rutaceae, Rosaceae, Leguminosae, and so forth (12,40). Flavanols, such as catechin, epicatechin, epigallocatechin, epicatechin gallate (ECG), and epigallocatechin gallate (EGCG), are also widespread in the medicinal herbs and dietary plants (e.g., tea, apples, berries, cocoa, and catechu) (4,40). Anthocyanins, including anthocyanidins (e.g., cyanidin, delphinidin, malvidin, peonidin, pelargonidin, etc.) and their glycosides, are widely distributed in the medicinal herbs such as inflorescences of Prunella vulgaris and flowers of Rosa chinensis (12). Many dietary plants (e.g., fruits, vegetables, grains, etc.) contain anthocyanins such as grape skins, blueberries, bayberry, red cabbages, beans, red/purple rice and corn, and purple sweet potatoes (32,40). Chalcones (butein, phloretin, sappanchalcone, carthamin, etc.) are detected in medicinal herbs such as Rhus verniciflua, Caesalpinia sappan, and Carthamus tinctorius (12,31).

Isoflavones include daidzein, genistein, glycinein, formononetin, and their glycosides (e.g., genistin, daidzin), mostly from soybeans, legumes, and red clover, and are also detected in the medicinal herbs of Leguminosae, such as roots of Astragalus mongholicus (12,31). In addition, biflavonoids are flavonoid dimers connected with a C–C or C–O–C bond (43) and occur in some fruits, vegetables, and medicinal plants such as Citrus fruits, Ginkgo biloba, Rhus succedanea, and Ouratea hexasperma (12,44,45). Silymarin (Fig. 3), a flavonoid analog, was found in fruits of Silybum marianum (46).

Tannins

Tannins are natural, water-soluble, polyphenolic compounds with molecular weight ranging from 500 to 4,000, usually classified into 2 classes: hydrolysable tannins (gallo- and ellagi-tannins) and condensed tannins (proanthocyanidins) (12)
The former are complex polyphenols, which can be degraded into sugars and phenolic acids through either pH changes or enzymatic or nonenzymatic hydrolysis. The basic units of hydrolysable tannins of the polyester type are gallic acid and its derivatives (4). Tannins are commonly found combined with alkaloids, polysaccharides, and proteins, particularly the latter (21). Hydrolysable tannins contain a central core of polyhydric alcohol such as glucose and hydroxyl groups, which are esterified either partially or wholly by gallic acid (gallotannins) or by hexahydroxy-diphenic acid or by other substituents (e.g., chebulic acid) (ellagitannins) (31). Ellagitannins differ from gallotannins in that at least 2 gallic acid units surrounding the core are linked through carbon-carbon bonds. Condensed tannins are structurally more complex and more widely spread
among the plants than hydrolysable tannins. They are mainly the oligomers and polymers (e.g., monomers, dimmers, and trimers) of flavan-3-diols (catechin or epicatechin derivatives), also known as proanthocyanidins (47). Some authors have considered that the polymerized products of flavan-3,4-diols also belong to the category of condensed tannins called leucoanthocyanidins (31). Complex tannins are constructed of catechin units linked glucosidically to gallotannin or ellagitannin; at least 2 gallic acid units surrounding the core are linked through carbon-carbon.
FIG. 4. The basic skeletons and structures of different categories of tannins from medicinal herbs and dietary plants.
Tannins are a large class of polyphenolics in dietary plants and medicinal herbs. Oligomeric proanthocyanidins, which are widely distributed in grape seed and skin and pine bark, are considered to be the most potent antioxidants and frequently used in health care and cancer treatment (48). Many fruits (e.g., apple juice, strawberries, longan, raspberries, pomegranate, walnuts, peach, blackberry, olive, and plum), vegetables (e.g., chickpeas, black-eyed peas, lentils, and haricot beans), and spices (e.g., clove and cinnamon) contain high levels of proanthocyanidins or ellagitannins (21,28). More than 32 species in 112 tested traditional Chinese medicinal plants associated with anticancer contain tannin constituents (e.g., gallotannins, ellagitannins, and proanthocyanidins) (12). Of these, 19 species contained particularly high proportions of tannins such as Chinese Galls, catechu, P. granatum, and S. officinalis. Ten of 126 Indian medicinal herbs also possess high levels of hydrolysable tannins (29). Some gallotannins were detected in Euphorbia hirta, Glycyrrhiza glabra, and Rhus succedanea. Several ellagitannins (e.g., corilagin, casuarictin) were isolated from fruits of T. chebula and peels of P. granatum. Camellia sinensis and Areca catechu contained proanthocyanidines and leucoanthocyanidins, respectively. Some plant species (e.g., Acca catechu, S. officinalis, Rosa chinensis, and P. granatum) may produce complex mixtures containing both hydrolysable and condensed tannins (12,29,31).

Stilbenes

Stilbenes are phenolic compounds displaying 2 aromatic rings linked by an ethane bridge, structurally characterized by the presence of a 1,2-diarylthene nucleus with hydroxyls substituted on the aromatic rings (4) (Fig. 5). They are distributed in higher plants and exist in the form of oligomers and in monomeric form (e.g., resveratrol, oxyresveratrol) and as dimeric, trimeric, and polymeric stilbenes or as glycosides. The well-known compound, trans-resveratrol, a phytoalexin produced by plants, is the member of this chemical family more abundant in the human diet (especially rich in the skin of red grapes), possessing a trihydroxystilben skeleton (21). We identified the monomeric stilbenes in 4 species of medicinal herbs, that is, trans-resveratrol in root of Polygonum cuspidatum, Polygonum multiflorum, and P. lactiflora; piceatannol in root of P. multiflorum; and oxyresveratrol in fruit of Morus alba (12,31). It was reported that dimeric stilbenes and stilbene glycosides were identified from these species (33,49). In addition, 40 stilbene oligomers were isolated from 6 medicinal plant species (Shorea hemsleyana, Vatica rassak, Vatica indica, Hopea utilis, Gnetum parvifolium, and Kobresia nepalensis) (50). Other stilbenes that have recently been identified in dietary source, such as piceatannol and its glucoside (usually named astringin) and pterostilbene, are also considered as potential chemopreventive agents (4). These and other in vitro and in vivo studies provide a rationale in support of the use of stilbenes as phytoestrogens to protect against hormone-dependent tumors (51).

Curcuminoids

Curcuminoids are ferulic acid derivatives, which contain 2 ferulic acid molecules linked by a methylene with a β-diketone structure in a highly conjugated system. Curcuminoids and ginerol analogues are natural phenolic compounds from plants of the family Zingiberaceae (12). Curcuminoids include 3 main chemical compounds: curcumin, demethoxycurcumin, and bis-demethoxycurcumin (31) (Fig. 5). All 3 curcuminoids impart the characteristic yellow color to turmeric, particularly to its rhizome, and are also major yellow pigments of mustard (3). Curcumínoids containing Curcuma longa (turmeric) and ginerol analogues containing Zingiber officinale (ginger) are not only used as Chinese traditional medicines but also as natural color agents or ordinary spices (12). In addition, curcuminoids with antioxidant properties were isolated from various Curcuma or Zingiber species, such as Indian medicinal herb Curcuma xanthorrhiza, the spice Curcuma domestica, Curcuma zedoaria grown in Brazil, and Zingiber cassumunar from tropic regions (29,52,53).

Coumarins

Coumarins are lactones obtained by cyclization of cis-ortho-hydroxycinnamic acid, belonging to the phenolics with the basic skeleton of C6+ C3(12) (Fig. 6). This precursor is formed through isomerization and hydroxylation of the structural analogs trans-hydroxycinnamic acid and derivatives.

FIG. 5. The structures of typical stilbenes and curcuminoids from medicinal herbs and dietary plants.
FIG. 6. The structures of representative coumarins and lignans from medicinal herbs and dietary plants.
Coumarins are present in plants in the free form and as glycosides. In general, coumarins are characterized by great chemical diversity, mainly differing in the degree of oxygenation of their benzopyrone moiety. In nature, most coumarins are C7-hydroxylated (4,31). Major coumarin constituents included simple hydroxycoumarins (e.g., aesculin, esculetin, scopoletin, and escopoletin), furocoumarins and isofurocoumarin (e.g., psoralen and isopsoralen from Psoralea corylifolia), pyrano coumarins (e.g., xanthyletin, xanthenoyl, seselin, khellactone, praecoptin A), bicoumarins, dihydro-isocoumarins (e.g., bergenin), and others (e.g., wedelolactone from Eclipta prostrata) (29–31). Plants, fruits, vegetables, olive oil, and beverages (coffee, wine, and tea) are all dietary sources of coumarins; for example, seselin from fruit of Seseli indicum, khellactone from fruit of Ammi visnaga, and praecoptin A from Peucedanum praetectorum (4,54). In our previous studies, we found coumarins occurred in the medicinal herbs Umbelliferae, Asteraceae, Convolvulaceae, Leguminosae, Magnoliaceae, Oleaceae, Rutaceae, and Ranunculaceae, such as simple coumarins from A. annua, furocoumarins (5-methoxyfuranocoumarin) from Angelica sinensis, pyranocoumarins from Citrus aurantium, and isocoumarins from Agrimonia pilosa (12). Some Indian medicinal plants (e.g., Toddalia aculeata, Murraya exotica, Foeniculum vulgare, and Carum coticum) and dietary spices (e.g., cumin and caraway) are also detected to possess coumarins (28,29). In addition, coumestans, derivatives of coumarin, including coumestrol, a phytoestrogen, are found in a variety of medicinal and dietary plants such as soybeans and Pueraria mirifica (http://en.wikipedia.org/wiki/).

Lignans

Lignans are also derived from cis-o-hydroxycinnamic acid and are dimers (with 2 C6-C3 units) resulting from tail–tail linkage of 2 conifer or sinapyl alcohol units (31) (Fig. 6). Lignans are mainly present in plants in the free form and as glycosides in a few (4). Main lignan constituents are lignanolides (e.g., arctigenin, arctin, secoisolariciresinol, and matairesinol from Arctium lappa), cyclolignanolides (e.g., chinisin from Polygala tenuifolia), bispoxylignans (e.g., forsythigenol and forsythin from Forsythia suspensa), neolignans (e.g., magnolol from Cedrus deodara and Magnolia officinalis), and others (e.g., schizandrin, schizatherin, and wulignan from Schisandra chinensis; pinoresinol from Pulsatilla chinensis; and furofuran lignans from Cuscuta chinensis) (12,29). The famous tumor therapy drug podophyllotoxin (cyclolignanolide) was first identified in Podophyllum peltatum, which Native Americans used to treat warts, and also found in a traditional medicinal plant Podophyllum emodi var. chinense (13). Two new lignans (podophyllotoxin glycodies) were isolated from the Chinese medicinal plant, Sinopodophyllum emodi (55). Different lignans (e.g., cubebin, hinokinin, yatein, and isoyatein) were identified from leaves, berries, and stalks of Piper cubeba L. (Piperaceae), an Indonesian medicinal plant (56). Milder et al. (57) established a lignan database from Dutch plant foods by quantifying lariresinol, pinoresinol, secoisolariciresinol, and matairesinol in 83 solid foods and 26 beverages commonly consumed in The Netherlands (37). They reported that flaxseed (mainly secoisolariciresinol), sesame seeds, and Brassica vegetables (mainly pinoresinol and lariresinol) contained unexpectedly high levels of lignans. Sesamol, sesamin, and their glucosides are also good examples of this type of compound, which come from sesame oil and sunflower oil (4).

Quinones

Natural quinones in the medicinal plants fall into 4 categories, that is, anthraquinones, phenanthraquinones, naphthoquinones, and benzoquinones (12) (Fig. 7). Anthraquinones are the largest class of natural quinones and occur more widely in the medicinal and dietary plants than other natural quinones (31). The hydroxyanthraquinones normally have 1 to 3 hydroxyl groups on the anthraquinone structure. Our previous investigation found that quinones were distributed in 12 species of medicinal herbs from 9 families such as Polygalaceae, Rubiaceae, Boraginaceae, Labiatae, Leguminosae, Myrsinaceae, and so forth (12,29). For example, high content benzoquinones and derivatives (embelin, embelinol, embeliaryl ester, embeliol) are found in Indian medicinal herbs Embelia ribes; naphthoquinones (shikonin, alkannan, and acetylshikonin) come from Lithospermum erythrorhizon and juglone comes from Juglans regia; phenanthraquinones (tanshinone I, IIa, and IIb) were detected in Salvia miltiorrhiza; denbinobin was detected in Dendrobium nobile; and many anthraquinones and their glycosides (e.g., rhein, emodin, chrysophanol, aloe-emodin, physcion, purpurin, pseudopurpurin, alizarin, munjistin, emodin-glucoside, emodin-malonyl-glucoside, etc.) were identified in the rhizomes and roots from P. cuspidatum (also in leaves), P. multiflorum, and R. officinale in the Polygalaceae and Rubia cordifolia in the Rubiaceae (12,29,33). In addition, some naphthoquinones were isolated from maize (Zea mays L.) roots (58).

Others

Because phenolic alkaloids, phenolic terpenoids (including aromatic volatile oils), special phenolic glycosides, and m-benzo-triphenol derivatives contain one or more aromatic rings bearing one or more hydroxy groups (Fig. 8), they also structurally belong to phenolic compounds and are widely distributed in medicinal herbs and dietary plants. There are different phenolic alkaloids detected in our previously investigated traditional Chinese medicinal plants such as Aconitum carmichaeli (e.g., demethylsalicine), Coptis chinensis (e.g., magnoflorine), Phel lodendron amurense (e.g., phelodendrine and magnoflorine), and Zanthoxyllum nitidum (e.g., nitidine and dihydronitidine) (12). Magnoflorine was also found in the traditional medical herbal tea, Toddalia asiatica Lam. in Okinawa (59). Some Chinese and Indian medicinal herbs and many spices contain high levels of various aromatic volatile oils or phenolic terpenoids
such as carnosic acid in *Andrographis paniculata*, *Nerium oleander*, *Xanthium sibiricum*, sweet basil, and sage; carnosol and epirosmanol in rosemary; carvacrol in oregano, sweet basil, and rosemary; anethole in star anise; menthol in mint; thymol in thyme; eugenol in clove; estragole and xanthoxylin in Chinese prickly ash; cinnamaldehyde in cinnamon; and triptophenolide and its methyl ether in *Tripterygium wilfordii* (12,28,29,60).

Additionally, simple phenols (only C₆ skeleton) are identified in the aromatic volatiles of some medicinal herbs such as vanillin and p-cresol from *A. sinensis* (12). Other phenolics also include syringaresinol (*Clematis chinensis*), paenol (*Paeonia suffruticosa*), m-benzo-triphenols (agrolin A, B from *A. pilosa*) and their derivatives (filicic acids from *Matteuccia struthiopteris*), and so forth. (12,28–31). Triptophenolide has been isolated from the roots of *T. wilfordii* Hook. Oleuropein and its glycoside have been obtained from olive oil (24).

**CANCER PREVENTION AND POSSIBLE MECHANISMS OF PHENOLIC COMPOUNDS FROM MEDICINAL HERBS AND DIETARY PLANTS**

Phenolic compounds from medicinal herbs and dietary plants possess a range of bioactivities and play an important role in prevention of cancer (Table 1). They have complementary and overlapping mechanisms of action including antioxidant activity and scavenging free radicals; modulation of carcinogen metabolism; regulation of gene expression on oncogenes and tumor suppressor genes in cell proliferation and differentiation; induction of cell-cycle arrest and apoptosis; inhibition of signal transduction pathways including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein-1 (AP-1), mitogen-activated protein kinases (MAPK), and others; modulation of enzyme activities in detoxification, oxidation, and reduction; anti-inflammatory properties by stimulation of the immune system; regulation of hormone metabolism; suppression of angiogenesis; antiatherosclerosis by inhibition proliferation and migration of vascular cells; neuroprotective effects on antiaging; antibacterial and antiviral effects; and action on other possible targets (4,19,21,61–114,117,118).

**Phenolic Acids and Analogs**

Phenolic acids and analogs possess broad bioactivities, some of which can play a role in cancer prevention. Most phenolic acids have antioxidant capacity, and the radical scavenging ability of phenolic acids depends on the number and position of hydroxyl groups and methoxy substituents in the molecules (31). In addition, phenolic acids and analogs can inhibit tumor cells and induce apoptosis by inducing cell cycle arrest; regulating signal transduction pathways; inducing or inhibiting some enzymes, and enhancing detoxification. And some phenolic acids and analogs also exhibit antibacterial, antifungal, antiviral, antimitagenic, and anti-inflammatory activities (21,64,67,74,82) (Table 1).

Gallic acid as a natural antioxidant had significant inhibitory effects on cell proliferation, induced apoptosis in a series of cancer cell lines, and showed selective cytotoxicity against tumor cells with higher sensitivity than normal cells (95). Cinnamic, caffeic, and ferulic acids and their esters inhibited the growth of bacteria and fungi, and hydroxytyrosol (an analog...
of phenolic acid) showed antimycoplasmal activity against Mycoplasma pneumoniae, Mycoplasma hominis, and Mycoplasma fermentans (64). In addition, hydroxytyrosol could inhibit cell proliferation and the activities of lipoxygenases (LOXs), increase catalase (CAT) and superoxide dismutase (SOD) activities, reduce leukotriene B4 production, decrease vascular cell adhesion molecule-1 (VCAM-1) mRNA and protein, slow the lipid peroxidation process, attenuate Fe^{2+}– and NO-induced cytotoxicity, and induce apoptosis by arresting the cells in the G0/G1 phase (96–98). Many phenolic acids and analogs possess anti-inflammatory effects and enhance immune function such as cinnamic acids, rosmarinic acid, gingerol, paradol, and hydroxytyrosol (4). Both chlorogenic acid and caffeic acids are antioxidants and inhibit the formation of mutagenic and carcinogenic N-nitroso compounds in vitro (21). Chlorogenic acid could also inhibit the formation of DNA single strand breaks and prevent the formation of dinitrogen trioxide by scavenging nitrogen dioxide generated in the human oral cavity (89). Furthermore, caffeic acids, capsaicin, and gingerol (an analog of phenolic acids) modulate the ceramide-induced signal transduction pathway, suppress the activation of NF-κB and AP1, and inhibit protein tyrosine kinase (PTK) activity (2,21,62). Gingerol could also inhibit tumor promotion, epidermal growth factor, tumor necrosis factor-alpha (TNF-α) production, and phorbol-12-myristate-13-acetate (PMA)-induced ornithine decarboxylase activity (2). Moreover, some phenolic acids (caffeic acid, ferulic acid, gallic acid, protocatechuic acid, etc.) in grape extracts and wine contribute to their activity against various types of cancer such as breast, lung, and gastric cancer (36).
Table 1: Cancer prevention and possible mechanisms of phenolic compounds from medicinal herbs and dietary plants

<table>
<thead>
<tr>
<th>Mechanisms of Action</th>
<th>Phenolic Compounds (Representative Phenolics)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant and antiaging activity</td>
<td>Phenolic acids and analogs (cafeic acid, gallic acid, chlorogenic acid, and ellagic acid), flavonoids (catechin and quercetin), tannins (proanthocyanidins, corilagin), stilbenes (resveratrol), curcuminoinds, coumarins, lignans, quinones, and others.</td>
<td>4,19,21,29,31, 34,63,95,108,111</td>
</tr>
<tr>
<td>Inhibit cell proliferation; inhibit oncogene expression; induce tumor suppressor gene expression; inhibit vascular endothelial growth factor.</td>
<td>Phenolic acids and analogs (chlorogenic acid and hydroxytyrosol), flavonoids and analogs (apigenin, daidzein, hesperetin, luteolin, kaempferol, myricetin, quercetin, EGCG, genistein, and silymarin), tannins (proanthocyanidins), stilbenes (resveratrol), curcuminoinds (curcumin), coumarins, lignans, quinones, and others.</td>
<td>4,21,101,103,110,118</td>
</tr>
<tr>
<td>DNA binding prevention</td>
<td>Flavonoids (methoxylated flavonoids and flavones), stilbenes (resveratrol), curcuminoids (curcumin), and quinones.</td>
<td>91,92</td>
</tr>
<tr>
<td>Enhancement of immune functions and surveillance</td>
<td>Phenolic acids and analogs (cinnamic acids, rosmarinic acid, gingerol, paradol, and hydroxytyrosol), flavonoids and analogs (apigenin, genistein, luteolin, quercetin, ECG, EGCG, and silymarin), tannins (proanthocyanidins, tannic acid), stilbenes (resveratrol), curcuminoinds (curcumin), coumarins (coumarin), lignans (sesamol), quinones, and others.</td>
<td>4,19,21,61,66–70</td>
</tr>
<tr>
<td>Phase I enzyme (block activation of carcinogens); COX-2; iNOS; XO; signal transduction enzymes, such as PKC and PTK; topoisomerase I and II; telomerase; urease; lipase; angiotensin I-converting enzyme; DNA methyltransferases (consequent reactivation of key tumor suppressor gene p16).</td>
<td>Phenolic acids and analogs (chlorogenic acid, cafeic acid, ellagic acid, and hydroxytyrosol), flavonoids and analogs (apigenin, luteolin, quercetin, and EGCG), tannins (proanthocyanidins, corilagin), stilbenes (resveratrol), curcuminoinds (curcumin), coumarins, lignans (podophyllotoxin), and quinones.</td>
<td>4,19,21,74–78,100</td>
</tr>
<tr>
<td>Phase II enzymes, such as UDP-glucuronosyl transferase and quinine reductases; glutathione peroxidase; catalase; SOD; cytochrome P450 epoxide hydrolase; NADPH:quinone reductase.</td>
<td>Phenolic acids and analogs (protocatechuic acid and ellagic acid), flavonoids (hesperidin and anthocyanins), tannins, stilbenes (resveratrol), curcuminoinds (curcumin), lignans, and quinones.</td>
<td>4,71–73</td>
</tr>
<tr>
<td>Inhibit expression of cell-adhesion molecules, namely ICAM-1 and VCAM-1; inhibit tumor cell invasion through Matrigel, cell migration, and cell proliferation.</td>
<td>Phenolic acids and analogs (hydroxytyrosol), flavonoids (baicalein, apigenin, and citrus flavonoids), stilbenes (resveratrol), curcuminoinds (curcumin), and lignans.</td>
<td>4,87,88,96–97</td>
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<thead>
<tr>
<th>Mechanisms of Action</th>
<th>Phenolic Compounds (Representative Phenolics)</th>
<th>References</th>
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<tbody>
<tr>
<td>Induction of cell differentiation</td>
<td>Flavonoids (apigenin), tannins (chebulinic acid), and coumarins.</td>
<td>79,80</td>
</tr>
<tr>
<td>Induction of cell-cycle arrest and induction of apoptosis</td>
<td>Phenolic acids (ferulic acid, caffeic acid and its phenethyl ester, ellagic acid, and hydroxytyrosol), flavonoids (quercetin and EGCG), tannins (proanthocyanidins, gallotannin and casuarinin), stilbenes (resveratrol), curcuminoids (curcumin), coumarins (coumarin and 7-hydroxycoumarin), lignans (sesamin),</td>
<td></td>
</tr>
<tr>
<td>Inhibit different cell cycles at different cell phases: G1, S, S/G2, and G2; direct</td>
<td>or indirect effect on cell cycle arrest; subsequently induce apoptosis, involving p53, the Bcl-2, and caspase families.</td>
<td>3,4,21,62,81–84,95</td>
</tr>
<tr>
<td>Nrf-KEAP1 (Kelch-like ECH-associated protein 1) complex signaling pathways; NF-κB</td>
<td>Phenolic acids and analogs (caffeic acid, gingerol, and capsaicin), flavonoids and analogs (apigenin, genistein, quercetin, EGCG, and silymarin), tannins (proanthocyanidins, ellagitannins), stilbenes (resveratrol), curcuminoids (curcumin), coumarins (esculetin), lignans, quinones (emodin), and others (anethole and carnosol).</td>
<td>2,4,19,21,61,</td>
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<tr>
<td>and AP-1 signaling pathway, including c-Jun activity suppression; the Wnt or β-</td>
<td></td>
<td>62,85,86,99,112</td>
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<td>catenin signaling pathway (direct inhibition of mitosis); MAPK signaling</td>
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<td>pathway; growth-factor receptor-mediated pathways</td>
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<tr>
<td>Some are important phytoestrogens; modulate the level of hormones; inhibit androgen</td>
<td>Phenolic acids and analogs (gossypol), flavonoids (isoflavones: formononetin, glycitein, genistein and daidzein), stilbenes (resveratrol), coumarins (coumestans: coumestrol), and lignans (pinosinol, lariciresinol, secoisolariciresinol, and matairesinol).</td>
<td>21,93,94,117</td>
</tr>
<tr>
<td>receptor effects in LNCaP prostate cancer cell</td>
<td></td>
<td></td>
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<tr>
<td>Inhibition of acrylamide, nitrosation, and nitration</td>
<td>Phenolic acids (caffeic acid and gallic acid), flavonoids (homoorientin, luteolin, quercetin, and EGCG), curcuminoids (curcumin), and others (eugenol).</td>
<td>65,89,90,113,114</td>
</tr>
<tr>
<td>Inhibit formation of acrylamide and heterocyclic amines, probable/possible human</td>
<td></td>
<td></td>
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<tr>
<td>carcinogens</td>
<td></td>
<td></td>
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<tr>
<td>Antiviral, antibacterial, and antifungal effects</td>
<td>Phenolic acids and analogs (cinnamic acid and its esters, and hydroxytyrosol), flavonoids, tannins, stilbenes (resveratrol), curcuminoids (curcumin), coumarins, lignans, quinones, and others.</td>
<td>21,64,105,106</td>
</tr>
<tr>
<td>Downregulate HIV expression, subsequently inhibit liver cancer</td>
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</table>

Abbreviations are as follows: ROS, reactive oxygen species; SOD, superoxide dismutase; TNF, tumor necrosis factor; LOX, lipoxigenases; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; XO, xanthine oxidase; PKC, protein kinase C; PTK, protein tyrosine kinase; UDP, NADPH, nicotinamide adenine dinucleotide phosphate; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; Bcl-2, B-cell non-Hodgkin lymphoma-2; nuclear factor kappa of activated B cells; AP-1, activator protein-1; MAPK, mitogen-activated protein kinases; LNCaP, lymph node carcinoma of the prostate; EGCG, epigallocatechin gallate; ECG, epicatechin gallate.
**Flavonoids**

Flavonoids have been linked to reducing the risk of major chronic diseases including cancer because they have powerful antioxidant activities in vitro, being able to scavenge a wide range of reactive species (e.g., hydroxyl radicals, peroxyl radicals, hypochlorous acid, and superoxide radicals) (42). Many flavonoids chelate transition metal ions such as iron and copper, decreasing their ability to promote reactive species formation. Flavonoids also inhibit bio-molecular damage by peroxynitrite in vitro, prevent carcinogen metabolic activation, induce apoptosis by arresting cell cycle, promote differentiation, modulate multidrug resistance, and inhibit proliferation and angiogenic process (42,71,72,91) (Table 1). These activities of flavonoids are related to their structures. Flavonoids containing more hydroxyl groups exhibit very high radical scavenging activity, for example, myricetin, quercetin, rutin, and quercitrin are well-known potent antioxidants. Flavonols with additional catechol structure (3-galloyl group) have significantly enhanced antiradical activity (31). Moreover, glycosylation of hydroxyl groups and substitution of other substituents (e.g., methoxy groups) also affects the antioxidant activity of flavonoids (34).

Many flavonoids possess diverse bioactivities. For example, apigenin could inhibit cell adhesion and invasion; reduce the formation of dioleopxide 2, mitochondrial proton FOF1-ATPase/ATP synthase, prostataglandyn synthase, and IL-6,8 (interleukin) production; block the expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin; and induce cell differentiation and interferon-gamma gene expression (79,87). Furthermore, genistein, luteolin, quercetin, ECG, EGCG, and silymarin as well as apigenin show antiangiogenesis and antimutagenic properties (62). Besides these 7 flavonoids and analogs, daidzein, hesperetin, kaempferol, and myricetin were all anti-inflammatory (21,46). In addition, apigenin, genistein, quercetin, EGCG, and silymarin could suppress the activation of NF-κB and AP1 and block signal transduction pathways (2,62,79,87). Silymarin also prevented induction of apoptosis and suppressed protein kinases and MAPKs (46). Soy isoflavone genistein was an angiogenesis inhibitor that could inhibit the growth of new blood vessels and showed antitumor and antiangiogenic activity in mouse models of melanoma and breast cancer (116). Moreover, some isoflavones (e.g., genistein and daidzein) were phytoestrogens and could mimic the biological activity of estrogens and modulate steroid hormone metabolism. Therefore, they might play an important role in breast cancer prevention (117).

Some catechins (e.g., EGCG and EGC) showed significant radical scavenging ability and could chelate metal ions and prevent the generation of free radicals. Their specific chemical structures (i.e., vicinal dihydroxy or trihydroxy structure) contribute to their potent antioxidant activity (31). EGCG could inhibit telomerase, LOXs, and DNA methyltransferase; reduce the expression of COX-2 (cyclooxygenase) and activation of NF-κB and AP1; block c-Jun N-terminal kinase (JNK) and p38 MAPK-related signaling pathways; attenuate adhesion and migration of peripheral blood CD8 T cells; increase eNOS (nitric oxide synthase) activity; and induce apoptosis by activating caspases and arresting cell growth G0/G1 phase of the cell cycle (2,4,21,99). Also, EGCG could induce apoptosis in human epidermoid carcinoma cells but not in normal human epidermal keratinocytes (99).

Quercetin is one of the most potent antioxidants and has antitumor, anti-inflammatory, antiproliferative, or apoptotic effects in vitro or in vivo. At molecular level, quercetin acts as an anticancer agent through modulation of cell cycle, protein, oncogenes, and antioncogenes (100). In addition, quercetin can inhibit the activity of caspases-3, protein kinases, telomerase, lymphocyte tyrosine kinase, different tyrosines, and serine-threonine kinases; increase the expression of nicotinamide adenine dinucleotide phosphate (NADPH):quinone oxidoreductase and activity of SOD, CAT, GSH; decrease lipoperoxidation, NO production and iNOS (inducible nitric oxide synthase) protein expression, and levels of some oxidative metabolites; prevent lactate dehydrogenase (LDH) leakage; interact with the β-catenin pathway; block c-Jun N-terminal kinase (JNK) and p38 MAPK-related signaling pathway; enhance Nrf2-mediated (NF-E2-related factor-2, a basic region-leucine zipper transcription factor to regulate transactivation of antioxidant genes) transcription activity; suppress angiogenesis, colorectal crypt cell proliferation; and induce apoptosis in different cell lines by arresting cell cycle (4,21,62,100).

**Tannins**

Hydrolysable tannins and condensed tannins are powerful antioxidant agents because they have many hydroxyl groups, especially many ortho-dihydroxy or galloyl groups. Bigger tannin molecules possess more galloyl and ortho-dihydroxy groups, and their activities are stronger (31). In addition, these tannins also exhibit strong antibacterial, antiulcer, anti-inflammatory, antileishmanial, antimutagenic, enzyme regulating, signal transduction pathways blocking, and apoptotic activities; thus, they have attracted wide attention for cancer treatment (68,75,82,85) (Table 1). For example, gallotannin showed anticarcinogenic activities in several animal models including colon cancer, and the hydrolysable tannin-containing fraction from Sweet Charlie strawberries was most effective at inhibiting mutation (101). In addition, 4 ellagittannins and 2 chromone gallates significantly blocked epidermal growth factor-induced cell transformation by attenuating AP-1 and phosphoinositide 3-kinases (PI3K) signaling pathways activation, and by inhibiting phosphorylation of extracellular-signal regulated protein kinases and p38 kinases (85). Chebulinic acid had an inhibitory effect on differentiation of human leukemia K562 cells through regulating transcriptional activation of erythroid related genes including gamma-globin, and NF-E2 genes, and through inhibiting acetylcholinesterase and hemoglobin synthesis (79). Casuarinin, a hydrolysable tannin isolated from the bark of *Terminalia arjuna* L. (Combretaceae), could inhibit the proliferation by blocking cell
cycle progression in the G0/G1 phase and by inducing apoptosis in human breast adenocarcinoma cells (81).

**Stilbenes**

Stilbenes, especially resveratrol, possess potential antioxidant, antibacterial, antiviral, anti-inflammatory, and anticancer activities (2,4,21,62,94) (Table 1). Resveratrol has increased in importance as a cancer preventive agent since 1997 (51). Resveratrol can affect the processes underlying all 3 stages of carcinogenesis, namely, tumor initiation, promotion, and progression. It had also been shown to suppress angiogenesis and metastasis. Extensive data in human cell cultures indicated that resveratrol could modulate multiple pathways involved in cell growth, apoptosis, and inflammation; and resveratrol and its hydroxylated analogues also possess antileishmanial activity (102,103). For molecular mechanisms of cancer prevention, resveratrol and its analogs could retard tumor progression by triggering numerous intracellular pathways leading to cell growth arrest such as inhibition of protein kinase C (PKC) activation; downregulation of β-catenin expression; counteraction of reactive oxygen species (ROS) production; activation of caspases; induction of genes for oxidative phosphorylation and mitochondrial biogenesis; and blocking NF-κB and AP1 mediated signal transduction pathways (51,94,102,103). Furthermore, resveratrol can inhibit the expression and function of the androgen receptor effects in LNCaP prostate cancer cell line by repressing androgen receptor upregulated genes (94). In addition, 40 stilbene oligomers possessed inhibitory activity against DNA topoisomerase II (50).

**Curcuminoinds**

Ongoing laboratory and clinical studies have indicated that curcuminoids possess unique antioxidant, anti-inflammatory, anticarcinogenic/amitmutagenic, antithrombotic, hepatoprotective, antifibrosis, antimicrobial, antiviral, and antiparasitic properties and play important roles in cancer chemotherapy (88,92,104) (Table 1). In particular, curcumin can suppress tumor promotion, proliferation, angiogenesis, and inflammatory signaling; decrease oxidatively modified DNA and the level of NOS mRNA and protein; modulate AP-1 signaling pathways; block phosphorylation and subsequent degradation of IκB kinase β activity; inhibit NF-κB-regulated gene products (cyclin D1, Bcl-2, Bcl-xL, COX-2); sustain phosphorylation of JNK and p38 MAPK; activate caspase-8, BID cleavage, and cytochrome c release; downregulate iNOS expression; upregulate Map kinase phosphates-5; and also has proapoptotic and antimetastatic activities (4,88,92). Tetrahydrocurcuminoid is a colorless hydrogenated product derived from the yellow curcuminoids and can be used as an efficient superior antioxidant mixture of compounds for use in achromatic foods and cosmetics (105). In addition, the ginerol analogues in ginger also had antioxidant activity (2).

**Coumarins**

Coumarins and derivatives possess diverse bioactivities, such as antioxidant, antitubercular, antimalarial, anti-HIV-1, antiangiogenesis, anti-mutagenic, anti-inflammatory, cell differentiation inducing, xanthine oxidase inhibiting, and cytotoxicity against human cancer cell lines (69,76,106) (Table 1). For example, coumarin and 7-hydroxycoumarin show antitumor actions in vitro and in vivo on human lung carcinoma cell lines by inhibiting cell proliferation, arresting cell cycle in the G phase, and inducing apoptosis (83). Esculetin (6,7-dihydroxycoumarin) showed lipoxygenase inhibitory effect on the proliferation response of cultured rabbit vascular smooth muscle cells by modulating P signal transduction pathway (86). The structure-activity relationship of esculetin and 8 other coumarin derivatives indicated that 2 adjacent phenolic hydroxyl groups at the C-6 and C-7 positions in the coumarin skeleton were necessary for the potent antiproliferative and antioxidant effect. Therefore, glycosylation and damage of the catechol structure (ortho-dihydroxy groups) had significant negative influence on the activity of the coumarins, for example, it considerably reduced the radical scavenging level (31).

**Lignans**

Some authors have reported that there was a beneficial effect of the hydroxyl group in the lignan molecules on the antioxidant activity and anticancer activity, but most of the lignans did not exhibit strong activity in scavenging radicals (31,63,107). Many reports also have shown that lignans could have anti-inflammatory, antibacterial, antiviral, antiallodynic, angiogenesis, and antimutagenic properties; regulate expression of enzymes, signal transduction pathways, and hormone metabolism; enhance detoxification; induce apoptosis by cell cycle arresting; and reduce human breast cancer cell adhesion, invasion, and migration in vitro (70,77,93) (Table 1). For example, sesamin had been reported to possess antioxidant, induction of apoptosis, cell cycle arresting, and anti-inflammatory effects and could be used in killing human leukemia, stomach, breast, and skin cancer cells (4). And podophyllotoxin was used in the treatment of cancer as a DNA topoisomerase II (topo II) inhibitor, because topo II induced DNA double-strand breaks and thus reduced torsion tension in DNA during replication and the condensation of chromosomes in the nucleus during cell division (13). In addition, lignans (e.g., pinoresinol, lariciresinol, secoisolariciresinol, and matairesinol) are also important phytosterogens (118).

**Quinones**

Quinones (especially hydroxyanthraquinones) are natural phenolic antioxidants. Among the hydroxyanthraquinones, purpurin, pseudopurpurin, and alizarin were most effective, and many others (e.g., emodin, chrysazine, rhein, chrysophanol, and aloë-emodin), without the ortho-dihydroxy structure, were far less effective (31). This indicated that the ortho-dihydroxy
structure in the hydroxanthraquinone molecules played a significant role in improving the radical scavenging capacity like the catechol structure in other phenolic molecules. In addition, glycosylation of hydroxanthraquinones markedly diminished their radical scavenging activity (108). Quinone metabolites perform a variety of key functions in plants including pathogen protection, oxidative phosphorylation, and redox signaling. Many of these structurally diverse compounds exhibit potent antimicrobial, anticancer, antioxidant, antiangiogenesis, antiinflammatory, and anti-inflammatory properties (109,110). Many studies have reported that some quinones (e.g., emodin) can prevent DNA binding, inhibit casein kinase-2 and urease, induce pRb-preventable G2/M cell cycle arrest and apoptosis, modulate the function of kinases, and block signal transduction pathways (13,66,78,84). Therefore, certain quinones can play an important role as biomarkers for cancer chemoprevention.

Others

Other phenolic compounds also present a wide range of bioactivities (Table 1). For example, magnoflorine from T. asiatica had anti-HIV activity; dihydroquinitidine possessed tumor specific cytotoxicity effects; triptophenololide had clear inhibitory effects on lymphocyte and IgG and Mn(II)-based oxidative radical cyclization reactions (111); oleuropein and its glycoside and carnosol had antioxidant, induction of apoptosis, cell cycle arresting, and anti-inflammatory effects; and anethole and carnosol suppressed AP-1 activation (59,61). Furthermore, eugenol exhibited potent antiproliferative activity at different stages of progression; induced apoptosis by blocking cells in the S phase of progression; inhibited E2F1 transcriptional activity in melanoma cells; and has been used as an antiseptic, antibacterial, analgesic agent in traditional medical practices in Asia (112).

Interestingly, natural phenolic compounds also suppress the formation of mutagenic and carcinogenic acrylamide and heterocyclic amines (65). High levels of acrylamide have been found after frying or baking of carbohydrate-rich foods such as potatoes and cereal products (113). Acrylamide has been classified as “probably carcinogenic to humans” by the International Agency for Research on Cancer. In earlier toxicological studies, acrylamide was genotoxic and carcinogenic to test animals and caused reproductive and developmental problems (65). Additionally, a series of heterocyclic amines (HCAs) have been isolated as mutagens from various kinds of thermally processed materials including cooked meat and fish and pyrolysis products of amino acids and proteins (113). Many HCAs have been demonstrated to be capable of forming DNA adducts to induce DNA damage, and some of them have been classified by the International Agency for Research on Cancer as probable/possible human carcinogens (113). Plant-derived extracts such as bamboo leaves, ginkgo, tea, grape seed extracts, and so forth, can reduce acrylamide in various heat-treated foods to varying extents (114). In addition, extracts from berries (e.g., blackberry, chokeberry, grape, and cherry), spices (e.g., thyme, marjoram, rosemary, sage, and garlic), soy, tea, and pine bark have significant effects on suppressing formation of both polar and nonpolar HCAs (90). Results showed that different antioxidant phenolic compounds in these plant extracts may play roles in reduction or inhibition of acrylamide and HCAs, subsequently reducing potential mutagenic/carcinogenic harm of certain cooked foods (113,114).

CONCLUSION

Phenolic compounds are ubiquitous and rich in medicinal herbs and dietary plants (e.g., fruits, vegetables, spices, cereals, and beverages). Various phenolic compounds possess a diverse range of beneficial biological activities, which contribute to their potential effects on inhibiting carcinogenesis. Extensive research has been conducted in vitro or in vivo on antioxidant and anticancer activities of phenolic compounds from medicinal herbs and dietary plants. Overwhelming clinical evidence has shown that chemoprevention by phenolic phytochemicals is an inexpensive, readily applicable, acceptable, and accessible approach to cancer control and management (3). However, more information about the health benefits and the possible risks of dietary supplement or herbal medicines is needed to ensure their efficacy and safety. In fact, toxic flavonoids and drug interactions, liver failure, dermatitis, and anemia were reported for some cases of polyphenol chemopreventive use (115). These potential toxic effects of phenolic compounds are strongly dependent on their concentration and chemical environment, which must be thoroughly understood before any preventive or therapeutic use is considered (4). However, information on safety assessment of natural phenolic compounds is still lacking.

In general, medicinal herbs and dietary plants are a good resource of bioactive phenolic compounds in cancer prevention, and only limited aspects have been investigated. There is still much work needed to search for novel and effective anticancer phenolic compounds from more medicinal and dietary plants, to further reveal mechanistic process, and to conduct confirmatory human clinical trials of these phenolic compounds in cancer prevention and treatment.

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