23.1 Introduction

Among the numerous products available from plants, the flavonoid superfamily plays a central role by its large number of molecules (over 6000) and also by the role these products occupy in the normal physiology of plants. Flavonoids are secondary plant metabolites involved in several biological processes (e.g., germination, UV protection, insecticides) and are also involved in the attraction of pollinating agents via the vivid colors of the anthocyanin pigments found in flowers (e.g., blue, purple, yellow, orange, and red) [1–3]. Flavonoids are found in the normal human diet composed of green vegetables, onions, fruits (apples, grapes, strawberries, etc.), beverages (coffee, tea, beer, red wine) [4, 5], and isoflavonoids are mainly found in soya bean-derived products [6].

Flavonoids are being studied intensely partly because of a renewed interest in medicinal plants used in folk medicine [7], and also because of the so-called “French paradox,” which is generally
thought to be linked to the Mediterranean diet (rich in fruits, vegetables, and red wine) which appears to protect against cardiovascular diseases in spite of its relatively high content in saturated fat [8]. In addition, several epidemiological studies have shown that diets rich in fruits and vegetables are generally associated with a lower cancer incidence [9–11].

The daily consumption of flavonoids is highly variable among different countries. Inasmuch as most of the human intake of flavonoids is based only on the consumption of a few flavonoids, the actual daily intake of flavonoids is probably superior to the reported estimates in the range of 3–68 mg/day, with a median value of 23 mg/day [12]. Other authors estimate the daily consumption of flavonoids (e.g., polyphenols) to be about 150–1000 mg/day [13]. A recent study in France has shown that fruits (mainly apples and strawberries) and vegetables (e.g., potatoes, lettuce, onions) account for about 28% of the daily intake in polyphenols, and that the total consumption would be over 300 mg/day [14]. Because fruits, vegetables, tea, coffee, and red wine are all rich in flavonoids, the focus of several research teams is now to identify which flavonoid is responsible for a given pharmacological effect and to better understand its molecular mechanism of action.

In this review, after a reminder of the flavonoid chemical structures, we briefly mention the main pharmacological activities of this class of compounds, and focus thereafter on the flavonoids of interest in the prevention and therapy of cancer.

### 23.2 Chemical Structures of Flavonoids

Flavonoids are composed of a 15 carbon atoms comprising 2 cycles of 6 carbon atoms linked by a 3 carbon chain (rings A and B, Fig. 23.1). Except for the chalcones and aurones, the 3 carbon bridge usually forms a benzo-γ-pyrone ring (ring C). All flavonoids are classified according to the substituents encountered on the different cycles and the saturation degree of the C ring. Three classes of flavonoids can be distinguished: the flavonoids (or 2-phenylbenzopyranes), the isoflavonoids (or 3-phenylbenzopyranes), and the
neoflavonoids (or the 4-phenylbenzopyranes) [15]. The flavonoids are further classified according to the structure of the C heterocycle (if present), in the following groups: flavones, flavanones, flavans, flavonols, chalcones, and anthocyanidins (Fig. 23.1).

In fruits and vegetables, flavonoids can be found as the free aglycones or more frequently linked with a sugar. The flavones and the flavonols (3-hydroxyflavones) are the most frequently found flavonoids (e.g., quercetin, kaempferol, myricetin, apigenin) (Fig. 23.2). Flavonones (e.g., naringenin), flavanols (e.g., catechin, dihydroflavanols, dihydrokaempferol, dihydroquercetin), and the dihydroflavan-3,4-diols (leucopelargonidol, leucocyanidol) have a natural distribution less important than flavones and flavonols. In nature, the flavonoids can also be found as biflavonoids which are O- or C-dimers of flavones, flavonols, flavanones, dihydroflavonols, and sometimes of isoflavones [16, 17].

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**Fig. 23.1** Main flavonoid classes

![Flavonoid Structures](image-url)
Flavonoid Metabolism

Natural flavonoids in their glycosidic forms are absorbed in the intestines. The glycosidic portion plays an important role in absorption, as was shown with quercetin glycosides which are better absorbed (52%) compared to the quercetin aglycone (24%) [18].

Flavonoid metabolism is considered to play an important role for the expression of its several biological activities [19]. The hepatic cytochrome P450s (CYP) can hydroxylate flavonoids often at the C5 and C6 positions on ring A, on C3 of ring C, and
also on C3’ and C4’ of ring B. In humans, CYP1A2, CYP3A4, and CYP2C9 are mostly involved in flavonoid hydroxylation [20]. Phase II metabolism (conjugation) involves glucuronidation, sulfatation, and methylation. The metabolism by the intestinal flora is also important and can lead to demethylation and ring fission [21]. Major differences in metabolism may exist between laboratory animals and humans, as was recently shown with the synthetic flavone-8-acetic acid which is thought to be activated in vivo in mice to anticancer active metabolites [22]. It was also recently shown that aminoflavone was activated to antiproliferative active metabolites through sulfatation [23].

23.4 Flavonoid Pharmacological Activities

Several mammalian enzymatic systems have been reported to be inhibited by flavonoids, for example, kinases, topoisomerase I, glutathione S-transferase, cytochrome P450s, aromatase, and so on. [24]. This large number of enzymatic systems affected by flavonoids is probably responsible for the rather large pharmacological activities reported for this class of agents that we briefly mention below before focusing on flavonoids as chemopreventive and chemotherapeutic anticancer agents.

Cardiovascular diseases: A recent study has shown that chronic administration of polyphenols from red wine in rats can prevent hypertension and vascular dysfunction [25]. In humans, a flavonoid-rich diet (e.g., tea, onion, apple, etc.) has been linked to a significant reduction in cardiovascular morbidity and mortality in several studies [26, 27]. Flavonoid and isoflavone intake were found to be the main phytochemicals contributing to the low incidence of coronary heart disease in Japanese women [28].

Antioxidant: Among the numerous pharmacological properties of flavonoids, their antioxidant action is probably the most studied. Free radicals such as the hydroxyl (OH\(^\bullet\)), the superoxide anion (O\(_2\)\(^\bullet\)), and the peroxylipidic radicals may be scavenged by flavonoids, mainly by the flavonoids bearing a C3 hydroxyl group (flavonols). Flavonoids can also chelate
metal ions. The antioxidant hypothesis is, however, being challenged because compounds with similar antioxidant properties may present different biological effects [29]. It has also been reported that flavonoids can also scavenge the NO radical [30]. This radical is formed by several cell types (e.g., endothelial cells and macrophages) and its release is due to the NO synthase activity which is important in vascular tone regulation. Because some flavonoids can inhibit cyclooxygenase, this could explain the quercetin effect in counteracting the vasodilatation of NO on the vascular endothelium [31, 32]. In this context, it is worth pointing out that some synthetic flavones have been reported to downregulate both iNOS expression and NO expression in leukemia cells [33].

Vascular protection: Polyphenols have been shown to increase the formation of NO by endothelial NO synthase. Flavonoids have also been shown to contribute to the normalization of the vascular permeability [34, 35].

Hepatoprotection: Flavonoid extracts from Silybum marianum have been used in folk medicine against liver diseases in the form of a complex mixture comprising silybin which would act on the hepatocyte membrane to prevent the uptake of toxic compounds and would stimulate hepatocyte regeneration [36]. The hepatoprotective effects of silybin and quercetin have been shown in the rat model administered a toxic dose of paracetamol (acetaminophen) [37].

Antiallergic: Certain flavonoids, for example, quercetin, can be antiallergenic by inhibiting enzymes involved in the histamine release from mastocytes and basophils (cAMP phosphodies- terase and Ca ++ ATPase) [38, 39].

Anti-inflammatory: The immune modulation of flavonoids appears to rely on their inhibition of eicosanoids and histamine formation and on their inhibition of free radical scavenging effects [40]. Several flavonoids can modify the metabolism of platelet arachidonic acid in vitro. Myricetin and quercetin can block cyclo-oxygenases and lipoxygenases action. Hesperidin is anti-inflammatory in a rat model of inflammation induced by carragenin or dextran. The interest in flavonoids as anti-inflammatory compounds is also
underlined by their lack of gastric toxicity frequently encountered with other anti-inflammatory drugs [24, 41].

**Antiulcer**: Some flavonoids can protect the gastric mucosa against ulcer-causing compounds. For example, hypolaetin-8-glucose, a flavonoid found in *Sideritis* species is considered as an active antiulcer compound. Naringin and quercetin are also antiulcerogen in the gastric ulceration induced by ethanol in the rat. The antiulcer properties of quercetin have been attributed to its mucus production activity [42]. In addition, quercetin can inhibit the growth of the ulcer-forming bacteria *Helicobacter pylori* and can decrease the production of chlorhydric acid by the gastric parietal cells [43].

**Antibacterial activity**: Several flavonoids have been shown to possess antibacterial activity, for example, apigenin, galangin, chrysin, naringin, epigallocatechin gallate, luteolin, quercetin, and kaempferol [44]. The activity of apigenin and galangin against both sensitive and antibiotic-resistant strains of *Staphylococcus aureus*, *Enterococcus faecium*, *Escherichia coli*, and *Pseudomonas aeruginosa*, is particularly noteworthy [45].

**Antiviral activity**: An important activity of some flavonoids is the inhibition of the human immunodeficiency virus (HIV). For example, acacetin, apigenin, baicalein, chrysin, hinokiflavone, myricetin, quercetagetin, robinetin, robustaflavone, and quercetin, were reported to be involved in HIV entry, infection, transcription, or replication in mammalian cells [46–50].

### 23.5 Flavonoids in Cancer Prevention

Numerous review articles have already been published concerning flavonoid involvement in the prevention of carcinogenesis and treatment of cancer [51–53, 24]. In the following paragraphs, we mainly focus on the mechanisms of action of flavonoids involved in cancer prevention and treatment. Figure 23.3 presents the main flavonoid actions potentially involved in the prevention and therapy of cancer.
23.5.1 In Vitro Antimutagenicity

Several flavonoids have been reported to be antimutagenic. Quercetin can inhibit the mutagenic effect of benzopyrene, a powerful carcinogen of the polycyclic aromatic hydrocarbon family, in bacterial systems of mutagenesis [54], and can also prevent the nuclear damages in mouse colon epithelial cells [55]. Galangin (3,5,7-trihydroxyflavone) and other flavonoids have shown anticlastogenic effects in vitro and in vivo in bleomycin or benzopyrene models [56]. Mutagenesis induced by diol-epoxide of benzopyrene (bay region) can also be inhibited by hydroxylated flavones [57]. Several synthetic flavones have also shown antimutagenic activity in the Ames test [58].

The prevention of carcinogenesis by flavonoids is thought to be due to the inhibition of a covalent bond between a reactive metabolite and DNA. It has been shown that polyphenols could prevent the covalent link between DNA and carcinogens (e.g., polycyclic aromatic hydrocarbons) by inhibiting enzymes involved in their activation, such as cytochrome P450s 1A1 and 1B1 [59–61]. In addition, the cytochromes’ P450s protein expression can be blocked by flavonoids thus preventing the formation of DNA reactive mutagens [62–64]. Flavonoids were also shown to induce phase 2 drug-metabolizing enzymes involved in carcinogens’ detoxification mechanisms, such as...
UDP-glucuronosyltransferase (UGT), NAD (P) H-quinone oxidoreductase, and glutathione S-transferase [65–67].

23.5.2 Cancer Prevention in Animal Models

Several flavonoids have been shown to prevent cancer in animal models [68]. Methoxylated flavones, for example, the 5,7-dimethoxyflavone and 3’,4’-dimethoxyflavone can prevent the formation of colon cancer at the initiation stage [61], and some synthetic 3-nitroflavones were also shown to prevent the formation of colon aberrant crypt foci in the rat model [69]. At the promotion stage, the 5,7-dimethoxyflavone and the 5,7,4’-trimethoxyflavone were found more active compared to their unmethylated counterpart, that is, chrysin and apigenin, respectively [70]. Anthocyanins can prevent colon cancer induced by 1,2-dimethylhydrazine [71].

Orally administered quercetin was shown to inhibit the DMBA-induced carcinogenesis in hamsters and rats [72, 73]. Likewise, orally administered flavone, flavanone, tangeretin and quercetin can inhibit the initiation and promotion of aflatoxin B1-induced hepatocarcinogenesis [74]. It has also been recently reported that orally administered fisetin, 2,2’-dihydroxychalcone or apigenin can significantly inhibit prostate cancer progression in TRAMP mice and prolong survival [75, 76]. Silybin is also active in the prevention and treatment of prostate cancer in animals and clinical studies are currently ongoing [77]. Silybin has been shown to prevent skin cancer in animal models, and its use in humans has been suggested because of its low toxicity [78]. Structure-activity relationships have shown that the ortho-dihydroxyphenyl on ring B appears essential for activity in the prevention of skin cancer [79]. Several green tea extracts have demonstrated the inhibition of skin carcinogenesis by oral ingestion or topical application [80, 81]. Compounds extracted from green tea such as epigallocatechin gallate (EGCG) and theaflavins can inhibit tumorigenesis induced by cisplatin and NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) [82, 83].

The mechanism of action of flavonoids with regard to their preventive effects of chemically induced cancers are generally attributed to their modulation of phase I and phase II metabolic enzymes,
thus preventing the formation of DNA-reactive species by cytochromes P450 and favoring their elimination by phase II enzymes (reviewed in [84]).

It is noteworthy that certain flavonoids and isoflavonoids can also exhibit activity in hormone-dependent mammary and prostate cancers. Aromatase, an enzyme involved in these cancers can be inhibited by flavonoids such as 7-methoxyflavone and 7,4′-dimethoxyflavone, which are potent inhibitors of this enzyme [85]. In addition, the inhibition of aromatase activity could result in a decrease of estrogenic levels in women and could be involved in the prevention of breast cancer [86]. Genistein and daidzein (isoflavones found in soya beans) can also inhibit hormone-dependent or independent mammary and prostate cancers in mice [87, 88]. Based on preclinical studies, Cross et al. have recently suggested the clinical use of phytoestrogens (e.g., genistein) in the prevention and therapy of colorectal, breast, and prostate cancers [89].

23.5.3 Cancer Prevention in Humans

Although the evidence supporting cancer prevention is still controversial in humans, probably because of the inherent difficulties to conduct this type of epidemiological studies, several reports have nonetheless shown beneficial effects of a polyphenol-rich diet in preventing certain types of cancer and to considerably lower the risk of dying from this disease [90].

In humans, important geographical differences in the incidence of prostate cancer appear to indicate that environmental factors are involved. Among these factors, a diet rich in polyphenols appears linked to a lower incidence of prostate cancer [91]. Results from several clinical studies indicate that soybean isoflavones administration appears to favorably affect prostate-specific antigen levels, and these observations should be an impetus for further clinical trials [92]. In addition, a recent large prospective study in European men found that higher concentrations of circulating genistein are indeed associated with a lower risk for prostate cancer [93].

Lung cancer incidence has also been reported to be lower in persons with high intake of flavonoids [94, 95]. A recent review of
epidemiological evidence has shown a small beneficial association between a lower incidence of lung cancer with tea and flavonoids consumption ([9], and references therein).

Epidemiological studies have long identified that breast cancer incidence is lowest in most Asian countries compared to Western countries, and that women of Asian origin eating a Western diet have the same breast cancer incidence as Western women. In breast cancer, it was also observed that the intake of flavones appears to protect against mammary tumors [11]. A recent study has also found that a dietary pattern characterized by frequent consumption of vegetables, fruits, fish, soybean curd, and low fat intake is associated with a reduced risk of breast cancer in Japanese women [96].

Ovarian cancer was also recently reported to be prevented by the consumption of tea and broccoli (containing kaempferol). If additional prospective studies confirm these results, this could lead to an important advance for ovarian cancer prevention [10].

Concerning the anthocyanins, these compounds were clearly shown to be cancer-protective in animal models, but human epidemiological studies have thus far not revealed a protective role of these molecules [97].

As stated above for the animal studies, the cancer-preventive effects of flavonoids in humans is also probably due to the modulation of phase I and phase II metabolic enzymes (reviewed in [84]). Also, the flavonoids could prevent cancer via their anti-inflammatory properties, because there is a growing consensus that inflammation probably plays a major role in cancer initiation [98].

23.6 Flavonoids in Cancer Therapy

23.6.1 Antimitotic Effects

Several authors have reported that certain flavonoids can interfere with tubulin polymerization in vitro and cause a cell arrest in mitosis [99–104]. The study of 79 flavonoid analogues of centaureidin (3,6,4’-trimethoxy-5,7,3’-trihydroxyflavone) has disclosed the structure-activity relationships (SAR) with regard to
cytotoxicity and interaction with tubulin: the most active compounds were the ones with hydroxyl groups at C3’ and C5, and also with methoxylated groups at C3 and C4’ [99].

Chalcones can also possess antimitotic activity, as demonstrated with the (E)-1-(2,5-dimethoxyphenyl)-3-[4-(dimethylamino) phenyl]-2-methyl-2-propene-1-one. This latter compound is active at only 4 nM in vitro in the HL60 human leukemia, and also in vivo in the B16 melanoma and L1210 leukemia models [105].

23.6.2 Apoptotic Effects

Catechins from green tea can induce prostate cancer cells apoptosis with the following order of potency: ECG (epicatechin-3-gallate) > EGCG (epigallocatechin-3-gallate) > EGC (epigallocatechin) > EC (epicatechin) [106]. Colon cancer cells can also enter apoptosis by exposure to baicalein, myricetin, genistein, and bavachanin [107]. B16 melanoma cells are mostly sensitive to chalcones: isoliquiritigenin > butein = phloretin [108]. Human HL60 leukemia cells are sensitive to apoptosis induced by apigenin, quercetin, myricetin, and kaempferol. EGCG has also been shown to cause cell death via a mechanism involving the inhibition of telomerase [109].

Quercetin-induced apoptosis appears to be due to a cell cycle arrest in S phase and to the inhibition of thymidilate synthase [110]. Another action of flavonoids on cancer cells is their effect on the thioredoxin system which exerts an antioxidant action and acts on cell proliferation and viability. This system is overexpressed in tumors, and it has recently been shown that myricetin and quercetin can inhibit this system with IC50 in the nanomolar range [111].

No clear-cut SARs are apparent for flavonoid induction of apoptosis, because the experimental data mentioned above seem to be highly dependent on the cancer cell line considered [53].

23.6.3 Differentiation

Kawai et al. have shown that HL60 human leukemia cells can undergo differentiation upon flavonoid exposure [112]. The
glycosides are less active than their corresponding aglycones, and the presence of the C2–C3 double bond is needed for activity, as well as a methoxy group in C3 and a catechol group on phenyl B. The most active flavonoids were the ones bearing the following substituents: 3-OH; 5,6,7,8,3',4'-OMe > 5,7,3',4'-OH > 5,6,7,8,4'-OMe [112]. Genistein, apigenin, luteolin, and quercetin were also found to induce HL60 cells differentiation [113]. Because the isoflavone genistein and its corresponding flavonoid apigenin are equipotent for the differentiation effect, the phenyl position in C2 or C3 position does not appear to be important for this activity. The double bond at the C2–C3 is needed for differentiation, as well as an unopened C ring because chalcones are inactive [113].

### 23.6.4 Topoisomerase Inhibition

Topoisomerases I and II are ubiquitous essential enzymes involved in DNA topology and are overexpressed in several tumors [114, 115]. Some flavonoids were reported to inhibit topoisomerase I, for example, EGCG, quercetin, fisetin, kaempferol, apigenin, and acacetin. SAR necessary for this anti-topoisomerase I activity is the absence of a sugar, a C2–C3 double bond, an oxo at C4, an hydroxyl at C3, C7 and C4', and 2 hydroxyl on phenyl B [116, 117, 114, 118–120].

Topoisomerase II can be inhibited by quercetin, quercetagetin, myricetin, baicalein, kaempferol, luteolin, fisetin, genistein, catechin, and EGCG [120, 121]. In addition to the double bond at C2–C3 and the C4 oxo, the presence of an hydroxyl group at the 5, 7, 3' and/or 4' positions is needed for topoisomerase II activity.

### 23.6.5 Multidrug Resistance

Multidrug resistance is a major problem encountered in cancer chemotherapy due to the overexpression of a membrane transport system of the ABC (P-glycoprotein, Pgp) type that can pump the anticancer agent out of the cell using ATP as energy source [122]. Because this resistance type concerns several classes of anticancer
drugs (e.g., anthracyclines, vinca alkaloids, taxanes, epipodophyllotoxins), the development of compounds that can inhibit this Pgp is important. Some flavonoids have been shown to modulate the Pgp, for example, quercetin, kaempferol, apigenin, myricetin, kaempferide, and naringenin [123, 124]. For this activity, a C5 hydroxy, a C4 oxo, and methoxy groups have been shown to be prerequisites.

A molecular mechanism of action for the reversal of multidrug resistance has been recently put forward involving the direct interaction of the flavonoid (EGCG) on the ATP binding site of a chaperone protein (GRP78) [125].

23.6.6 Cell Signaling

As alluded to above, most of the flavonoid therapeutic effects have been attributed to their antioxidant properties. However, the exact mechanisms involved in the biological actions of flavonoids are only partly understood, and the classical view of the antioxidant action of flavonoids to explain their pharmacological actions is challenged by several authors [126].

Indeed, several observations indicate that flavonoids could exert their action through other mechanisms independent of their antioxidant effect. For example, contrary to in vitro experimental systems where the aglycone is almost exclusively studied, flavonoids are extensively metabolized in vivo, and their redox potential is therefore modified. It now appears plausible that flavonoid bioactive forms may not be the initial compounds found in plants (e.g., aglycones and their glycosides), but instead their metabolites formed after intestinal absorption and hepatic metabolism [19].

For example, several flavonoids first undergo a deglycosylation in the intestine and then a phase II hepatic metabolism to glucuronide, sulfate, and O-methylated metabolites. In addition, modifications by the intestinal flora are known to modify further the flavonoids to phenolic acids which can also be reabsorbed and be further metabolized in the liver. All these metabolic transformations lead to a drastic decrease of their classical antioxidant potential [126]. Moreover, the concentrations of flavonoids and their
metabolites found in vivo in plasma and tissues are relatively low (in the nanomolar range) compared to other natural antioxidant molecules such as ascorbic acid and alpha-tocopherol which are found at micromolar concentrations.

The above observations on the metabolism of flavonoids have led several authors to consider that flavonoids could exert their cellular effects via their interaction with key proteins involved in the intracellular signal transduction cascade instead than by their antioxidant properties [127]. Flavonoids were shown to act on the MAP kinase (mitogen-activated protein kinase) signaling pathway [128], and other [129] signaling pathways such as the phosphoinositide 3-kinase (PI 3-kinase), the Akt/protein kinase B (Akt/PKB), the tyrosine kinases, and the protein kinase C (PKC) (reviewed in [126]). The inhibition or stimulation of these pathways can profoundly affect cellular functions by altering the phosphorylation status of key target molecules or modifying the expression of certain genes.

It now appears that flavonoids are biomolecules which are acting through modulation of cell signaling instead of being merely antioxidant molecules and that a better understanding of these mechanisms is needed in order (it is hoped) to improve their therapeutic effects in cancer.

23.6.7 Effect on Hormone-Dependent Cancers

As mentioned above, epidemiological studies have shown that soy isoflavones present in the diet of several Asian countries are probably playing an important role in the lower incidence of breast and prostate cancers. Genistein, the major isoflavone found in soy-based foods has been found to inhibit carcinogenesis in animal models through its antagonist action of estrogen- and androgen-mediated signaling pathways (reviewed in [130]). Other flavonoids have also been identified as chemopreventive compounds in prostate cancer including the dietary agents such as green tea, pomegranate, lupeol, fisetin, and delphinidin [131]. Fisetin has also been shown to inhibit androgen receptor signaling and human prostate tumor growth in athymic nude mice [132].
23.6.8 Antiangiogenic Properties

Since the seminal article by Folkman in 1971 [133] which contributed to identify tumor angiogenesis as a key and essential player in metastasis and tumor growth, angiogenesis has become the target of several approaches aimed at preventing the formation of new vessels in tumors or attempting to destroy existing tumor vasculature.

Flavonoids have been shown to inhibit angiogenesis in vitro at micromolar concentrations, for example, 3-hydroxyflavone, 3’,4’-dihydroxyflavone, 2’,3’-dihydroxyflavone, fisetin, apigenin, and luteolin [134]. SAR studies have shown that a C4 oxo and a C2–C3 double bond are needed for antiangiogenic activity. Genistein was also shown to possess antiangiogenic properties [130, 135].

The mechanism of the antiangiogenic action by flavonoids involves the inhibition of the expression of VEGF (vascular endothelial growth factor) and HIF-1 (hypoxia-inducible factor-1) [136]. In addition, it has recently been shown that EGCG could decrease the VEGF mRNA and significantly reduce the growth of gastric tumors [137]. Synthetic flavonoids have also been shown to inhibit aminopeptidase N and to inhibit angiogenesis [138, 139]. The inhibition of NO synthase has also been shown to be involved in the inhibition of angiogenesis by quercetin in vitro and in vivo [140].

Endothelial cells were shown to be particularly responsive to flavonoid action. For example, fisetin, quercetin, kaempferol, apigenin, and morin were recently shown to induce the formation of cell extensions and filopodias at noncytotoxic concentrations and that this morphological alteration was linked to a cytoskeletal stabilization [141]. These flavonoid morphological modifications may also be linked to the inhibition of tubulin polymerization [100] and also with interaction with actin polymerization [142]. Fisetin has also been recently found to inhibit angiogenesis in vitro and also in a murine lung tumor in vivo [143].

23.6.9 Vascular Disrupting Properties

Vascular disrupting agents are low molecular weight compounds that selectively destroy tumor vasculature while they leave normal
vasculature intact. This vascular disruption causes a shutdown in blood flow to solid tumors resulting in extensive tumor cell necrosis [144]. This flavonoid action is particularly important considering that most tumors are unfortunately detected when they already have developed an important vascular system. Some synthetic flavonoids have shown vascular disrupting activity, for example, flavone-8-acetic acid and its analogue DMXAA (5,6-dimethylxanthenone-4-acetic acid) which is now undergoing clinical testing ([145] and references therein). These vascular disrupting flavonoids appear to act through local cytokine production, but their exact mechanism of action is still debated [144].

### 23.6.10 Flavonoids Combination with Cancer Treatments

Several groups have reported the beneficial effects of combining flavonoids with anticancer drug treatments. Genistein was shown to reverse radio- and chemo-resistance in cancer chemotherapy [130], and also to increase the effect on hormone-independent human prostate cancer cells [146]. Genistein was also found to be synergistic with 5-aza-deoxycytidine, a potent DNA methylation inhibitor, in leukemia cell lines [147]. Genistein can also act synergistically with several other drugs such as tamoxifen, cisplatin, 1,3-bis 2-chloroethyl-1-nitrosourea (BCNU), dexamethasone, daunorubicin, and tiazofurin [148].

A synergistic effect of silibinin on growth inhibition, reversal of chemo-resistance, apoptosis induction, and a strong increase in G2-M checkpoint arrest was observed when given in combination with several chemotherapeutic drugs [149]. Silibinin was also reported to restore sensitivity to paclitaxel-resistant human ovarian carcinoma cells [150]. It was also recently observed that fisetin combined with cyclophosphamide can lead to a synergistic anticancer activity in Lewis lung carcinoma-bearing mice [143].

Although most data indicate that flavonoids can advantageously be combined with chemotherapeutic agents in order to increase efficacy and also with the aim to decrease toxicities, care should nonetheless be recommended. For example, an antagonistic effect was recently reported with the combination of the proteasome inhibitor
bortezomib with green tea polyphenols, where it was noted that the anticancer agent’s effect was negated by the flavonoids [151].

23.7 Flavonoid Toxicity

Flavonoids are considered as safe compounds, because unwanted toxic effects in humans are not frequently encountered. Some cases of hemolytic anemia have been reported with catechin and its metabolites which can bind to erythrocytes and cause an immune reaction which disappears upon treatment discontinuation [152]. Some flavonoids can generate quinones that may be involved in contact sensibilization. However, flavonoids can be considered as weak allergens, because humans are frequently in contact with this type of compounds in their alimentation [153].

Flavonoids can be administered in humans at relatively high doses because of their low toxicity. For example, a phase I study has been conducted with quercetin administered as a rapid intravenous injection every 3 weeks in cancer patients, and the maximal tolerated dose was found to be as high as 1700 mg/m² where nephrotoxicity was observed, but without myelosuppression, with a phase 2 recommended dose of 1400 mg/m² [154]. Of interest, this study has shown an anticancer effect in a case of hepatocarcinoma and in an ovarian cancer case. Flavonoids can therefore be considered as relatively nontoxic compounds in man.

23.8 Concluding Remarks and Future Directions

Flavonoids can be regarded as compounds possessing clearcut pharmacological activities in a variety of diseases, and also in cancer prevention and treatment, as was demonstrated in various in vitro and in vivo preclinical systems. However, few flavonoids have emerged thus far in the clinical setting in relation to their potential use in cancer prevention and/or treatment. This is probably due to the fact that most clinical studies have tried to mimic the high-dose regimens usually employed in cytotoxic therapies, and that
flavonoids would perhaps need to be administered at metronomic dosages, that is, at low doses over a long period of time.

Because of the poor oral bioavailability of flavonoids and other polyphenols in their aglycone forms, much work needs to be accomplished to overcome this serious problem before the use of these agents could be recommended as nutraceuticals in humans. The design of prodrugs that could be better absorbed is currently under way [155]. The permethylation of polyphenols could also be helpful to increase their metabolic stability [156]. Pharmaceutical formulations of flavonoids as nanoemulsions or liposomes could also be helpful to improve their bioavailability and potentially increase their efficacy in vivo.

In the meantime, it is advisable to suggest that the regular consumption of fruits and vegetables is beneficial to prevent cancer as was shown by several epidemiological studies in humans. Some authors have suggested that a mixed flavonoid diet may be better than the ingestion of specific flavonoids [157]. However, concerning the combination of flavonoids with existing cancer chemotherapeutic regimens, extreme care should be the rule for the present time before more preclinical data are available, because antagonism between anticancer molecules and flavonoids is always possible, especially with new chemotherapeutic regimens [151].

Although several plants and spices containing flavonoids have been used for thousands of years in traditional Eastern medicine, and also in spite of the important preclinical data demonstrating the efficacy of this class of compounds in prevention and therapy of cancer, this class of nontoxic agents has yet to gain its place in Western medicine [24]. Based on the growing interest of the scientific community in the study of natural products use in medicine, it seems likely that the next decade will see the emergence of new improved flavonoids, because this class of compounds offers an almost unlimited resource for new cancer drug discovery.

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References

1. Harborne JB. Nature, distribution, and function of plant flavonoids. In: Cody V, Middleton EJr, Harborne JB, editors. Plant flavonoids in biology and medicine – Biochemical, pharmacological, and structure-activity relationships. New York: Alan R. Liss, Inc; 1986. pp. 15–24.
2. Havsteen BH. The biochemistry and medical significance of the flavonoids. Pharmacol Ther. 2002;96:67–202.
3. Winkel-Shirley B. Biosynthesis of flavonoids and effects of stress. Curr Opin Plant Biol. 2002;5:218–23.
4. Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79:727–47.
5. US Department of Agriculture. Database for the flavonoid content of selected foods – Release 2.1. Beltsville, Maryland, USA; 2007. http://www.ars.usda.gov/nutrientdata
6. US Department of Agriculture. Database for the isoflavone content of selected foods – Release 2.0. Beltsville, Maryland, USA, 2008. http://www.ars.usda.gov/nutrientdata
7. Di Carlo G, Mascolo N, Izzo AA, Capasso F. Flavonoids: old and new aspects of a class of natural therapeutic drugs. Life Sci. 1999;65:337–53.
8. Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K, van Leeuwen PA. Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr. 2001;74:418–25.
9. Arts IC. A review of the epidemiological evidence on tea, flavonoids, and lung cancer. J Nutr. 2008;138:1561S–66S.
10. Gates MA, Tworoger SS, Hecht JL, De V, I, Rosner B, Hankinson SE. A prospective study of dietary flavonoid intake and incidence of epithelial ovarian cancer. Int J Cancer 2007;121:2225–32.
11. Peterson J, Lagiou P, Samoli E, Lagiou A, Katsouyanni K, La Vecchia C, Dwyer J, Trichopoulos D. Flavonoid intake and breast cancer risk: a case-control study in Greece. Br J Cancer 2003;89:1255–9.
12. Aherne SA, O’Brien NM. Dietary flavonols: chemistry, food content, and metabolism. Nutrition 2002;18:75–81.
13. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr. 2000;130:2073S–85S.
14. Brat P, George S, Bellamy A, Du CL, Scalbert A, Mennen L, Arnault N, Amiot MJ. Daily polyphenol intake in France from fruit and vegetables. J Nutr. 2006;136:2368–73.
15. Marais JPJ, Deavours B, Dixon RA, Ferreira D. The stereochemistry of flavonoids. In: Grotewold E, editor. The science of flavonoids. New York: Springer Science, Inc; 2006. pp. 1–46.
16. Ghedira K. Les flavonoïdes: structure, propriétés biologiques, rôle prophylactique et emplois en thérapeutique (Flavonoids: structure, biological activities, prophylactic function and therapeutic uses). Phytothérapie 2005;4:162–9.

17. Iwashina T. The structure and distribution of the flavonoids in plants. J Plant Res. 2000;113:287–99.

18. Hollman PC, Katan MB. Dietary flavonoids: intake, health effects and bioavailability. Food Chem Toxicol. 1999;37:937–42.

19. Spencer JP, Kuhnle GG, Williams RJ, Rice-Evans C. Intracellular metabolism and bioactivity of quercetin and its in vivo metabolites. Biochem J. 2003;372:173–81.

20. Breinholt VM, Offord EA, Brouwer C, Nielsen SE, Brosen K, Friedberg T. In vitro investigation of cytochrome P450-mediated metabolism of dietary flavonoids. Food Chem Toxicol. 2002;40:609–16.

21. Manach C, Donovan JL. Pharmacokinetics and metabolism of dietary flavonoids in humans. Free Radic Res. 2004;38:771–85.

22. Pham MH, Auzeil N, Regazzetti A, Dauzonne D, Dugay A, Menet M-C, Scherman D, Chabot GG. Identification of new flavone-8-acetic acid metabolites using mouse microsomes and comparison with human microsomes. Drug Metab Dispos. 2007;35:2023–34.

23. Meng LH, Shankavaram U, Chen C, Agama K, Fu HQ, Gonzalez FJ, Weinstein J, Pommier Y. Activation of aminoflavone (NSC 686288) by a sulfotransferase is required for the antiproliferative effect of the drug and for induction of histone γ-H2AX. Cancer Res. 2006;66:9656–64.

24. Middleton E Jr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacol Rev. 2000;52:673–751.

25. Jimenez R, Lopez-Sepulveda R, Kadmiri M, Romero M, Vera R, Sanchez M, Vargas F, O’Valle F, Zarzuelo A, Duenas M, Santos-Buelga C, Duarte J. Polyphenols restore endothelial function in DOCA-salt hypertension: role of endothelin-1 and NADPH oxidase. Free Radic Biol Med. 2007;43:462–73.

26. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen elderly study. Lancet 1993;342:1007–11.

27. Nair S, Gupta R. Dietary antioxidant flavonoids and coronary heart disease. J Assoc Physicians India 1996;44:699–702.

28. Arai Y, Watanabe S, Kimira M, Shimoi K, Mochizuki R, Kinae N. Dietary intakes of flavonols, flavones and isoflavones by japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. J Nutr. 2000;130:2243–50.

29. Andriambeloson E, Kleschyov AL, Muller B, Beretz A, Stoclet JC, Andriantsitohaina R. Nitric oxide production and endothelium-dependent vasorelaxation induced by wine polyphenols in rat aorta. Br J Pharmacol. 1997;120:1053–8.

30. Huk I, Brovkovych V, Nanobash VJ, Weigel G, Neumayer C, Partyka L, Patton S, Malinski T. Bioflavonoid quercetin scavenges superoxide and
increases nitric oxide concentration in ischaemia-reperfusion injury: an experimental study. Br J Surg. 1998;85:1080–5.

31. Duarte J, Jimenez R, O’Valle F, Galisteo M, Perez-Palencia R, Vargas F, Perez-Vizcaino F, Zarzuelo A, Tamargo J. Protective effects of the flavonoid quercetin in chronic nitric oxide deficient rats. J Hypertens. 2002;20:1843–54.

32. van Acker SA, Tromp MN, Haenen GR, van der Vijgh WJ, Bast A. Flavonoids as scavengers of nitric oxide radical. Biochem Biophys Res Commun. 1995;214:755–9.

33. Quiney C, Dauzonne D, Kern C, Fourneron JD, Izard JC, Mohammad RM, Kolb JP, Billard C. Flavones and polyphenols inhibit the NO pathway during apoptosis of leukemia B-cells. Leuk Res. 2004;28:851–61.

34. Stoclet JC, Chataigneau T, Ndiaye M, Oak MH, El Bedoui J, Chataigneau M, Schini-Kerth VB. Vascular protection by dietary polyphenols. Eur J Pharmacol. 2004;500:299–313.

35. Ursini F, Tubaro F, Rong J, Sevanian A. Optimization of nutrition: polyphenols and vascular protection. Nutr Rev. 1999;57:241–9.

36. Valenzuela A, Guerra R. Protective effect of the flavonoid silybin dihemsuccinate on the toxicity of phenylhydrazine on rat liver. FEBS Lett. 1985;181:291–4.

37. Gilani AH, Janbaz KH, Shah BH. Quercetin exhibits hepatoprotective activity in rats. Biochem Soc Trans. 1997;25:S619.

38. Amella M, Bronner C, Briancon F, Haag M, Anton R, Landry Y. Inhibition of mast cell histamine release by flavonoids and biflavonoids. Planta Med. 1985;51:16–20.

39. Formica JV, Regelson W. Review of the biology of quercetin and related bioflavonoids. Food Chem Toxicol. 1995;33:1061–80.

40. Wang HB, Yao H, Bao GH, Zhang HP, Qin GW. Flavone glucosides with immunomodulatory activity from the leaves of Pleioblastus amarus. Phytochemistry 2004;65:969–74.

41. Sanchez dM, Vera B, Galvez J, Zarzuelo A. Effect of quercitrin on the early stages of hapten induced colonic inflammation in the rat. Life Sci. 2002;70:3097–108.

42. Martin MJ, Marhuenda E, Perez-Guerrero C, Franco JM. Antiulcer effect of naringin on gastric lesions induced by ethanol in rats. Pharmacology 1994;49:144–50.

43. Shin JE, Kim JM, Bae EA, Hyun YJ, Kim DH. In vitro inhibitory effect of flavonoids on growth, infection and vacuolation of Helicobacter pylori. Planta Med. 2005;71:197–201.

44. Cushnie TP, Lamb AJ. Antimicrobial activity of flavonoids. Int J Antimicrob Agents 2005;26:343–56.

45. Cushnie TP, Hamilton VE, Lamb AJ. Assessment of the antibacterial activity of selected flavonoids and consideration of discrepancies between previous reports. Microbiol Res. 2003;158:281–9.

46. Critchfield JW, Butera ST, Folks TM. Inhibition of HIV activation in latently infected cells by flavonoid compounds. AIDS Res Hum Retroviruses 1996;12:39–46.
47. Fesen MR, Pommier Y, Leteurtre F, Hiroguchi S, Yung J, Kohn KW. Inhibition of HIV-1 integrase by flavones, caffeic acid phenethyl ester (CAPE) and related compounds. Biochem Pharmacol. 1994;48:595–608.

48. Li BQ, Fu T, Dongyan Y, Mikovits JA, Ruscetti FW, Wang JM. Flavonoid baicalin inhibits HIV-1 infection at the level of viral entry. Biochem Biophys Res Commun. 2000;276:534–8.

49. Lin YM, Anderson H, Flavin MT, Pai YH, Mata-Greenwood E, Pengsupar P, Pezzuto JM, Schinazi RF, Hughes SH, Chen FC. In vitro anti-HIV activity of biflavonoids isolated from Rhus succedanea and Garcinia multiflora. J Nat Prod. 1997;60:884–8.

50. Xu HX, Wan M, Dong H, But PP, Foo LY. Inhibitory activity of flavonoids and tannins against HIV-1 protease. Biol Pharm Bull. 2000;23:1072–6.

51. Cazarolli LH, Zanatta L, Alberton EH, Figueiredo MS, Folador P, Dama-zio RG, Pizzolatti MG, Silva FR. Flavonoids: prospective drug candidates. Mini Rev Med Chem. 2008;8:1429–40.

52. Li Y, Fang H, Xu W. Recent advance in the research of flavonoids as anticancer agents. Mini Rev Med Chem. 2007;7:663–78.

53. Lopez-Lazaro M. Flavonoids as anticancer agents: structure-activity relationship study. Curr Med Chem Anticancer Agents 2002;2:691–714.

54. Ogawa S, Hirayama T, Mohara M, Tokuda M, Hirai K, Fukui S. The effect of quercetin on the mutagenicity of 2-acetylaminofluorene and benzo[a]pyrene in Salmonella typhimurium strains. Mutat Res. 1985;142:103–7.

55. Wargovich MJ, Neng VW, Newmark HL. Inhibition by plant phenols of benzo[a]pyrene-induced nuclear aberrations in mammalian intestinal cells: a rapid in vivo assessment method. Food Chem Toxicol. 1985;23:47–9.

56. Heo MY, Sohn SJ, Au WW. Anti-genotoxicity of galangin as a cancer chemopreventive agent candidate. Mut Res/Rev Mut Res. 2001;488:135–50.

57. Huang MT, Wood AW, Newmark HL, Sayer JM, Yagi H, Jerina DM, Conney AH. Inhibition of the mutagenicity of bay-region diol-epoxides of polycyclic aromatic hydrocarbons by phenolic plant flavonoids. Carcinogenesis 1983;4:1631–7.

58. Beudot C, De Meo MP, Dauzonne D, Elias R, Laget M, Guiraud H, Balansard G, Dumenil G. Evaluation of the mutagenicity and antimutagenicity of forty-two 3-substituted flavones in the Ames test. Mutat Res. 1998;417:141–53.

59. Doostdar H, Burke MD, Mayer RT. Bioflavonoids: selective substrates and inhibitors for cytochrome P450 CYP1A and CYP1B1. Toxicology 2000;144:31–8.

60. Guengerich FP, Chun YJ, Kim D, Gillam EM, Shimada T. Cytochrome P450 1B1: a target for inhibition in anticarcinogenesis strategies. Mutat Res. 2003;523–24:173–82.

61. Wen X, Walle T. Preferential induction of CYP1B1 by benzo[a]pyrene in human oral epithelial cells: impact on DNA adduct formation and prevention by polyphenols. Carcinogenesis 2005;26:1774–81.
62. Ciolo-H, Wang TT, Yeh GC. Diosmin and diosmetin are agonists of the aryl hydrocarbon receptor that differentially affect cytochrome P450 1A1 activity. Cancer Res. 1998;58:2754–60.
63. Tsuji PA, Walle T. Inhibition of benzo[a]pyrene-activating enzymes and DNA binding in human bronchial epithelial BEAS-2B cells by methoxylated flavonoids. Carcinogenesis 2006;27:1579–85.
64. Wen X, Walle UK, Walle T. 7-Dimethoxyflavone downregulates CYP1A1 expression and benzo[a]pyrene-induced DNA binding in Hep G2 cells. Carcinogenesis 2005;26:803–9.
65. Chou FP, Chu YC, Hsu JD, Chiang HC, Wang CJ. Specific induction of glutathione S-transferase GSTM2 subunit expression by epigallocatechin gallate in rat liver. Biochem Pharmacol. 2000;60:643–50.
66. Galijatovic A, Otake Y, Walle UK, Walle T. Induction of UDP-glucuronosyltransferase UGT1A1 by the flavonoid chrysir in Caco-2 cells – potential role in carcinogen bioactivation. Pharm Res 2001;18:374–9.
67. Gross-Steinmeyer K, Stapleton PL, Liu F, Tracy JH, Bammler TK, Quigley SD, Farin FM, Buhler DR, Safe SH, Strom SC, Eaton DL. Phytochemical-induced changes in gene expression of carcinogen-metabolizing enzymes in cultured human primary hepatocytes. Xenobiotica 2004;34:619–32.
68. Lambert JD, Hong J, Yang GY, Liao J, Yang CS. Inhibition of carcinogenesis by polyphenols: evidence from laboratory investigations. Am J Clin Nutr. 2005;81:284S–91S.
69. Steele VE, Boone CW, Dauzonne D, Rao CV, Bensasson RV. Correlation between electron-donating ability of a series of 3-nitroflavones and their efficacy to inhibit the onset and progression of aberrant crypt foci in the rat colon. Cancer Res. 2002;62:6506–9.
70. Walle T, Ta N, Kawamori T, Wen X, Tsuji PA, Walle UK. Cancer chemopreventive properties of orally bioavailable flavonoids – methylated versus unmethylated flavones. Biochem Pharmacol. 2007;73:1288–96.
71. Hagiwara A, Yoshino H, Ichihara T, Kawabe M, Tamano S, Aoki H, Koda T, Nakamura M, Imaida K, Ito N, Shirai T. Prevention by natural food anthocyanins, purple sweet potato color and red cabbage color, of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-associated colorectal carcinogenesis in rats initiated with 1,2-dimethylhydrazine. J Toxicol Sci. 2002;27:57–68.
72. Balasubramanian S, Govindasamy S. Inhibitory effect of dietary quercetin on 7,12-dimethyl-benz[a]anthracene-induced hamster buccal pouch carcinogenesis. Carcinogenesis 1996;17:877–9.
73. Verma AK, Johnson JA, Gould MN, Tanner MA. Inhibition of 7,12-dimethylbenz[a]anthracene and N-nitosomethylurea-induced rat mammary cancer by dietary flavonol quercetin. Cancer Res. 1988;48:5754–8.
74. Siess MH, Le Bon AM, Canivenc-Lavier MC, Suschetet M. Mechanisms involved in the chemoprevention of flavonoids. Biofactors 2000;12:193–9.
75. Haddad A, Venkateswaran V, Klotz L, Fleschner N. A mixed flavonoid diet reduces prostate tumor progression in TRAMP mice. Proc Amer Assoc Cancer Res. 2007;48:2585.
76. Shukla S, Maclennan GT, Flask CA, Fu P, Mishra A, Resnick MI, Gupta S. Blockade of beta-catenin signaling by plant flavonoid apigenin suppresses prostate carcinogenesis in TRAMP mice. Cancer Res. 2007;67:6925–35.

77. Singh RP, Agarwal R. Prostate cancer prevention by silibinin. Curr Cancer Drug Targets 2004;4:1–11.

78. Katiyar SK. Silymarin and skin cancer prevention: anti-inflammatory, antioxidant and immunomodulatory effects (Review). Int J Oncol. 2005;26:169–76.

79. Hou DX, Kai K, Li JJ, Lin S, Terahara N, Wakamatsu M, Fujii M, Young MR, Colburn N. Anthocyanidins inhibit activator protein 1 activity and cell transformation: structure-activity relationship and molecular mechanisms. Carcinogenesis 2004;25:29–36.

80. Khan WA, Wang ZY, Athar M, Bickers DR, Mukhtar H. Inhibition of the skin tumorigenicity of the (+/-)-7-beta,8 alpha-dihydroxy-9 alpha, 10 alpha-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene by tannic acid, green tea polyphenols and quercetin in Sencar mice. Cancer Lett. 1988;42:7–12.

81. Yang CS, Maliakal P, Meng X. Inhibition of carcinogenesis by tea. Annu Rev Pharmacol Toxicol. 2002;42:25–54.

82. Xu Y, Ho CT, Amin SG, Han C, Chung FL. Inhibition of tobacco-specific nitrosamine-induces lung tumorigenesis in A/J mice by green tea and its major polyphenol as antioxidants. Cancer Res. 1992;52:3875–9.

83. Yang GY, Liu Z, Seril DN, Liao J, Ding W, Kim S, Bondoc F, Yang CS. Black tea constituents, theaflavins, inhibit 4-(methylnitrosamino)-1-(3-pyr-idyl)-1-butanone (NNK)-induced lung tumorigenesis in A/J mice. Carcinogenesis 1997;18:2361–5.

84. Ren W, Qiao Z, Wang H, Zhu L, Zhang L. Flavonoids: promising anticancer agents. Med Res Rev. 2003;23:519–34.

85. Ta N, Walle T. Aromatase inhibition by bioavailable methylated flavones. J Steroid Biochem Mol Biol. 2007;107:127–9.

86. Chen S, Zhang F, Sherman MA, Kijima I, Cho M, Yuan YC, Toma Y, Osawa Y, Zhou D, Eng ET. Structure-function studies of aromatase and its inhibitors: a progress report. J Steroid Biochem Mol Biol. 2003;86:231–7.

87. Mentor-Marcel R, Lamartiniere CA, Eltoum IE, Greenberg NM, Elgavish A. Genistein in the diet reduces the incidence of poorly differentiated prostatic adenocarcinoma in transgenic mice (TRAMP). Cancer Res. 2001;61:6777–82.

88. Wang W, Heideman L, Chung CS, Pelling JC, Koehler KJ, Birt DF. Dietary genistein suppresses chemically induced prostate cancer in Lobund-Wistar rats. Cancer Lett. 2000;186:11–18.

89. Cross HS, Kallay E, Lechner D, Gerdenitsch W, Adlercreutz H, Armbrecht HJ. Phytoestrogens and vitamin D metabolism: a new concept for the prevention and therapy of colorectal, prostate, and mammary carcinomas. J Nutr. 2004;134:1207S–12S.

90. Hertog MG, Bueno-de-Mesquita HB, Fehily AM, Sweetnam PM, Elwood PC, Kromhout D. Fruit and vegetable consumption and cancer mortality in the Caerphilly Study. Cancer Epidemiol Biomarkers Prev. 1996;5:673–7.
91. Guy L, Remesy C, Demigne C, Boiteux J-P. Nutrition et cancer de prostate. Progrès en Urologie 2000;10:505–12.
92. Messina M, Kucuk O, Lampe JW. An overview of the health effects of isoflavones with an emphasis on prostate cancer risk and prostate-specific antigen levels. J AOAC Int. 2006;89:1121–34.
93. Travis RC, Spencer EA, Allen NE, Appleby PN, Roddam AW, Overvad K, et al. Plasma phyto-oestrogens and prostate cancer in the European Prospective Investigation into Cancer and Nutrition. Br J Cancer 2009;100:1817–23.
94. Knekt P, Jarvinen R, Seppanen R, Hellovaara M, Teppo L, Pukkala E, Aromaa A. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. Am J Epidemiol. 1997;146:223–30.
95. Mursu J, Nurmi T, Tuomainen TP, Salonen JT, Pukkala E, Voutilainen S. Intake of flavonoids and risk of cancer in Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. Int J Cancer 2008;123:660–3.
96. Hirose K, Matsuo K, Iwata H, Tajima K. Dietary patterns and the risk of breast cancer in Japanese women. Cancer Sci. 2007;98:1431–8.
97. Wang LS, Stoner GD. Anthocyanins and their role in cancer prevention. Cancer Lett. 2008;269:281–90.
98. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436–44.
99. Beutler JA, Hamel E, Vlietinck AJ, Haemers A, Rajan P, Roitman JN, Cardellina JH, Boyd MR. Structure-activity requirements for flavone cytotoxicity and binding to tubulin. J Med Chem. 1998;41:2333–8.
100. Gupta K, Panda D. Perturbation of microtubule polymerization by quercetin through tubulin binding: a novel mechanism of its antiproliferative activity. Biochemistry 2002;41:13029–38.
101. Hadfield JA, Ducki S, Hirst N, McGown AT. Tubulin and microtubules as targets for anticancer drugs. Prog Cell Cycle Res. 2003;5:309–25.
102. Lawrence NJ, McGown AT. The chemistry and biology of antimitotic chalcones and related enone systems. Curr Pharm Des. 2005;11:1679–93.
103. Lichius JJ, Thoison O, Montagnac A, Pais M, Gueritte-Voegelein F, Sevenet T, Cosson JP, Hadi AH. Antimitotic and cytotoxic flavonols from Zieridium pseudobtusifolium and Acronychia porteri. J Nat Prod. 1994;57:1012–6.
104. Shi Q, Chen K, Li L, Chang JJ, Autry C, Kozuka M, Konoshima T, Estes JR, Lin CM, Hamel E. Antitumor agents, 154. Cytotoxic and antimitotic flavonols from Polanisia dodecandra. J Nat Prod. 1995;58:475–82.
105. Edwards ML, Stemrick DM, Sunkara PS. Chalcones: a new class of antimitotic agents. J Med Chem. 1990;33:1948–54.
106. Chung LY, Cheung TC, Kong SK, Fung KP, Choy YM, Chan ZY, Kwok TT. Induction of apoptosis by green tea catechins in human prostate cancer DU145 cells. Life Sci. 2001;68:1207–14.
107. Kuntz S, Wenzel U, Daniel H. Comparative analysis of the effects of flavonoids on proliferation, cytotoxicity, and apoptosis in human colon cancer cell lines. Eur J Nutr. 1999;38:133–42.
108. Iwashita K, Kobori M, Yamaki K, Tsushida T. Flavonoids inhibit cell growth and induce apoptosis in B16 melanoma 4A5 cells. Biosci Biotechnol Biochem. 2000;64:1813–20.

109. Naasani I, Seimiya H, Tsuruo T. Telomerase inhibition, telomere shortening, and senescence of cancer cells by tea catechins. Biochem Biophys Res Commun. 1998;249:391–6.

110. Haghiac M, Walle T. Quercetin induces necrosis and apoptosis in SCC-9 oral cancer cells. Nutr Cancer 2005;53:220–31.

111. Lu J, Papp LV, Fang J, Rodriguez-Nieto S, Zhivotovsky B, Holmgren A. Inhibition of mammalian thioredoxin reductase by some flavonoids: implications for myricetin and quercetin anticancer activity. Cancer Res. 2006;66:4410–18.

112. Kawaii S, Tomono Y, Katase E, Ogawa K, Yano M. Effect of citrus flavonoids on HL-60 cell differentiation. Anticancer Res. 1999;19:1261–9.

113. Takahashi T, Kobori M, Shinmoto H, Tsushida T. Structure-activity relationships of flavonoids and the induction of granulocytic- or monocytic-differentiation in HL60 human myeloid leukemia cells. Biosci Biotechnol Biochem. 1998;62:2199–204.

114. Berger SJ, Gupta S, Belfi CA, Gosky DM, Mukhtar H. Green tea constituent (−)-epigallocatechin-3-gallate inhibits topoisomerase I activity in human colon carcinoma cells. Biochem Biophys Res Commun. 2001;288:101–5.

115. Cardellini E, Durban E. Phosphorylation of human topoisomerase I by protein kinase C in vitro and in phorbol 12-myristate 13-acetate-activated HL-60 promyelocytic leukaemia cells. Biochem J. 1993;291(Pt 1):303–7.

116. Ahmad N, Feys DK, Nieminen AL, Agarwal R, Mukhtar H. Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. J Natl Cancer Inst. 1997;89:1881–6.

117. Ahmad N, Gupta S, Mukhtar H. Green tea polyphenol epigallocatechin-3-gallate differentially modulates nuclear factor kappaB in cancer cells versus normal cells. Arch Biochem Biophys. 2000;376:338–46.

118. Boege F, Straub T, Kehr A, Boesenberg C, Christiansen K, Andersen A, Jakob F, Kohrle J. Selected novel flavones inhibit the DNA binding or the DNA religation step of eukaryotic topoisomerase I. J Biol Chem. 1996;271:2262–70.

119. Chowdhury AR, Sharma S, Mandal S, Goswami A, Mukhopadhyay S, Majumder HK. Luteolin, an emerging anti-cancer flavonoid, poisons eukaryotic DNA topoisomerase I. Biochem J. 2002;366:653–61.

120. Constantinou A, Mehta R, Runyan C, Rao K, Vaughan A, Moon R. Flavonoids as DNA topoisomerase antagonists and poisons: structure-activity relationships. J Nat Prod. 1995;58:217–25.

121. Austin CA, Patel S, Ono K, Nakane H, Fisher LM. Site-specific DNA cleavage by mammalian DNA topoisomerase II induced by novel flavone and catechin derivatives. Biochem J. 1992;282(Pt 3):883–9.

122. Gottesman MM. How cancer cells evade chemotherapy: sixteenth Richard and Hinda Rosenthal Foundation Award Lecture. Cancer Res. 1993;53:747–54.
123. de Wet H, McIntosh DB, Conseil G, Baubichon-Cortay H, Krell T, Jault JM, Daskiewicz JB, Barron D, Di Pietro A. Sequence requirements of the ATP-binding site within the C-terminal nucleotide-binding domain of mouse P-glycoprotein: structure-activity relationships for flavonoid binding. Biochemistry 2001;40:10382–91.

124. Hooijberg JH, Broxterman HJ, Heijn M, Fles DL, Lankelma J, Pinedo HM. Modulation by (iso) flavonoids of the ATPase activity of the multidrug resistance protein. FEBS Lett. 1997;413:344–8.

125. Ermakova SP, Kang BS, Choi BY, Choi HS, Schuster TF, Ma WY, Bode AM, Dong Z. (-)-Epigallocatechin gallate overcomes resistance to etoposide-induced cell death by targeting the molecular chaperone glucose-regulated protein 78. Cancer Res. 2006;66:9260–9.

126. Williams RJ, Spencer JP, Rice-Evans C. Flavonoids: antioxidants or signalling molecules? Free Radic Biol Med. 2004;36:838–49.

127. Schroeter H, Boyd C, Spencer JPE, Williams RJ, Cadenas E, Rice-Evans C. MAPK signaling in neurodegeneration: influences of flavonoids and of nitric oxide. Neurobiol Aging 2002;23:861–80.

128. Kobuchi H, Roy S, Sen CK, Nguyen HG, Packer L. Quercetin inhibits inducible ICAM-1 expression in human endothelial cells through the JNK pathway. Am J Physiol. 1999;277:C403–C411.

129. Kong AN, Yu R, Chen C, Mandlekar S, Primiano T. Signal transduction events elicited by natural products: role of MAPK and caspase pathways in homeostatic response and induction of apoptosis. Arch Pharm Res. 2000;23:1–16.

130. Banerjee S, Li Y, Wang Z, Sarkar FH. Multi-targeted therapy of cancer by genistein. Cancer Lett. 2008;269:226–42.

131. Syed DN, Suh Y, Afaq F, Mukhtar H. Dietary agents for chemoprevention of prostate cancer. Cancer Lett. 2008;265:167–76.

132. Khan N, Asim M, Afaq F, Abu ZM, Mukhtar H. A novel dietary flavonoid fisetin inhibits androgen receptor signaling and tumor growth in athymic nude mice. Cancer Res. 2008;68:8555–63.

133. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971;285:1182–6.

134. Fotsis T, Pepper MS, Aktas E, Breit S, Rasku S, Adlercreutz H, Wahala K, Montesano R, Schweiger L. Flavonoids, dietary-derived inhibitors of cell proliferation and in vitro angiogenesis. Cancer Res. 1997;57:2916–21.

135. Fotsis T, Pepper M, Adlercreutz H, Fleischmann G, Hase T, Montesano R, Schweiger L. Genistein, a dietary-derived inhibitor of in vitro angiogenesis. Proc Natl Acad Sci USA 1993;90:2690–4.

136. Liu LZ, Fang J, Zhou Q, Hu X, Shi X, Jiang BH. Apigenin inhibits expression of vascular endothelial growth factor and angiogenesis in human lung cancer cells: implication of chemoprevention of lung cancer. Mol Pharmacol. 2005;68:635–43.

137. Zhu BH, Zhan WH, Li ZR, Wang Z, He YL, Peng JS, Cai SR, Ma JP, Zhang CH. Epigallocatechin-3-gallate inhibits growth of gastric cancer by
reducing VEGF production and angiogenesis. World J Gastroenterol. 2007;13:1162–9.

138. Bauvois B, Puiffe ML, Bongui JB, Paillat S, Monneret C, Dauzonne D. Synthesis and biological evaluation of novel flavone-8-acetic acid derivatives as reversible inhibitors of aminopeptidase N/CD13. J Med Chem. 2003;46:3900–13.

139. Bauvois B, Dauzonne D. Aminopeptidase-N/CD13 (EC 3.4.11.2) inhibitors: chemistry, biological evaluations, and therapeutic prospects. Med Res Rev. 2006;26:88–130.

140. Jackson SJT, Venema RC. Quercetin inhibits eNOS, microtubule polymerization, and mitotic progression in bovine aortic endothelial cells. J Nutr. 2006;136:1178–84.

141. Touil YS, Fellous A, Scherman D, Chabot GG. Flavonoid-induced morphological modifications of endothelial cells through microtubule stabilization. Nutr Cancer 2009;61:310–21.

142. Bohl M, Tietze S, Sokoll A, Madathil S, Pfennig F, Apostolakis J, Fahmy K, Gutzeit HO. Flavonoids affect actin functions in cytoplasm and nucleus. Biophys J. 2007;93:2767–80.

143. Touil YS, Seguin J, Scherman D, Chabot GG. Synergistic antiangiogenic and antitumoral effects of the combination of the flavonoid fisetin and cyclophosphamide in Lewis lung carcinoma bearing mice. Proc Amer Assoc Cancer Res. 2009;50:1008(Abstract 4591).

144. Tozer GM, Kanthou C, Baguley BC. Disrupting tumour blood vessels. Nat Rev Cancer 2005;5:423–35.

145. Gridelli C, Rossi A, Maione P, Rossi E, Castaldo V, Sacco PC, Colantuoni G. Vascular disrupting agents: a novel mechanism of action in the battle against non-small cell lung cancer. Oncologist 2009;14:612–20.

146. Chang KL, Cheng HL, Huang LW, Hsieh BS, Hu YC, Chih TT, Shyu HW, Su SJ. Combined effects of terazosin and genistein on a metastatic, hormone-independent human prostate cancer cell line. Cancer Lett. 2009;276:14–20.

147. Raynal NJ, Charbonneau M, Momparler LF, Momparler RL. Synergistic effect of 5-Aza-2’-deoxycytidine and genistein in combination against leukemia. Oncol Res. 2008;17:223–30.

148. Ravindranath MH, Muthugounder S, Presser N, Viswanathan S. Anticancer therapeutic potential of soy isoflavone, genistein. Adv Exp Med Biol. 2004;546:121–65.

149. Raina K, Agarwal R. Combinatorial strategies for cancer eradication by silybinin and cytotoxic agents: efficacy and mechanisms. Acta Pharmacol Sin. 2007;28:1466–75.

150. Zhou L, Liu P, Chen B, Wang Y, Wang X, Internati MC, Wachtel MS, Frezza EE. Silybinin restores paclitaxel sensitivity to paclitaxel-resistant human ovarian carcinoma cells. Anticancer Res. 2008;28:1119–27.

151. Golden EB, Lam PY, Kardosh A, Gaffney KJ, Cadenas E, Louie SG, Petasis NA, Chen TC, Schonthal AH, Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors. Blood 2009;113:5927–37.
152. Salama A, Mueller-Eckhardt C. Cianidanol and its metabolites bind tightly to red cells and are responsible for the production of auto- and/or drug-dependent antibodies against these cells. Br J Haematol. 1987;66:263–6.

153. Schmalle HW, Jarchow OH, Hausen BM, Schulz K-H. Aspects of the relationships between chemical structure and sensitizing potency of flavonoids and related compounds. In: Cody V, Middleton E, Harborne JB, editors. Plant flavonoids in biology and medicine: biochemical, pharmacological, and structure-activity relationships. New York: Alan R. Liss, Inc; 1986. pp. 387–90.

154. Ferry DR, Smith A, Malkhandi J, Fyfe DW, deTakats PG, Anderson D, Baker J, Kerr DJ. Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for in vivo tyrosine kinase inhibition. Clin Cancer Res. 1996;2:659–68.

155. Hirpara KV, Aggarwal P, Mukherjee AJ, Joshi N, Burman AC. Quercetin and its derivatives: synthesis, pharmacological uses with special emphasis on anti-tumor properties and prodrug with enhanced bio-availability. Anticancer Agents Med Chem. 2009;9:138–61.

156. Walle T, Wen X, Walle UK. Improving metabolic stability of cancer chemoprotective polyphenols. Expert Opin Drug Metab Toxicol. 2007;3:379–88.

157. Liu RH. Potential synergy of phytochemicals in cancer prevention: mechanism of action. J Nutr. 2004;134:3479S–85S.