Chapter 2
Effect of Flavonoids from Fruits and Vegetables in the Prevention and Treatment of Cancer

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Abstract Cancer is the major health problem worldwide over a century. The development of cancer is a multi-step process, including initiation, promotion and progression. This process is driven by genetic changes, elicit transformation of initiated cell into cancerous cell with abnormal proliferative and invasive capabilities, and ultimately distant metastasis. Recent studies also exhibit that chronic inflammation is implicated in tumorigenesis by over-production of inflammatory mediators and creation of an inflammatory microenvironment. Prevention and treatment of cancer through dietary intervention has been considered as a rational approach. Convincing evidence shows regular consumption of fruit and vegetables is associated with reduced risks of cancer. Flavonoids are widely present in diet such as fruits and vegetables, they have been demonstrated a broad spectrum of biological activities for human health. They have been found to interfere with cancer development at different stage by targeting on various signaling molecules, genes, proteins and enzymes involved in tumorigenesis. Accumulating evidences report the potential of dietary flavonoids for both chemopreventive and chemotherapeutic effects which act on regulation of redox status, cellular proliferation, differentiation, programmed cell death, inflammation angiogenesis and metastasis. Some of them display synergy effect in combination of conventional therapies for drug-resistant cancer cells. In this chapter, we summarize recent knowledge and the underlying mechanism on chemopreventive and chemotherapeutic activities of dietary flavonoids that may offer effective approach for the control of cancer incidence.

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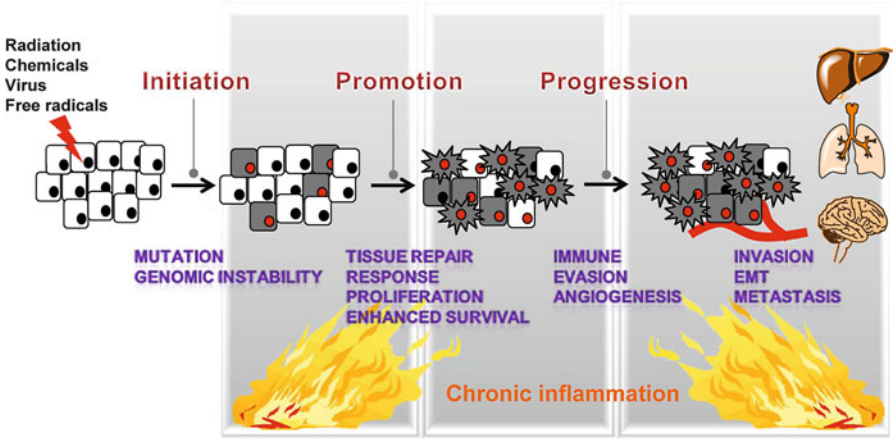


Fig. 2.1 Development of cancer is a multiple step, including initiation, promotion and progression process

2.1 Cancer Development

Cancer is the major leading cause of death worldwide. Numerous researches show that cancer development in humans is a multistep process. In 2000, Hanahan and Weinberg (2000) proposed that tumorigenesis acquires six biological capabilities including sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Recently, several lines of evidence also reveal that chronic inflammation is the seventh hallmark of cancer (Hanahan and Weinberg 2011). Tumorigenesis has been characterized by three critical steps including initiation, promotion and progression in many types of human cancers (Fig. 2.1). This process can be activates by any one of the various environmental carcinogens, inflammatory agents, tumor promoters and reactive oxygen species (ROS) (Pan and Ho 2008; Shields and Harris 1991).

- Initiation stage: it begins with DNA damage in a cell population exposed to various environmental carcinogens, free radicals, inflammatory agents, and tumor promoters. The most relevant in this regard are mutations activating proto-oncogenes and inactivating tumor suppressor genes, such as *c-myc* and *p53*, or increase of genomic instability in damaged cells.
- Promotion stage: it could be defined as a process of escape programmed cell death with enhanced survival property of initiated cells (with mutated gene) that results in clonal expansion and further producing nodules, polyps or papillomas.
- Progression stage: this stage is characterized by the transformation of pre-neoplastic cells into malignant tumor invading surrounding tissues and forming metastases by enhanced angiogenesis, epithelial-mesenchymal transition (EMT) immune suppression/evasion capabilities.

In progress of clinical technology and medicine development, cancer diagnosis, surgical techniques, and adjuvant therapies are greatly improved, but still with limitation on reduction of cancer incidence and mortality. The major problem in current cancer therapy is the eventual development of recurrent or metastatic cancers caused by drug resistance in most patients (Alexander and Friedl 2012). Scientists have proposed and identified many critical molecules involved in tumorigenesis in past few decades. A number of genes with genetic mutation or loss of function, dysregulation of signaling molecules, proteins and enzymes are contributes to cancer development (Tonon 2008; William et al. 2009). However, despite understanding of the process and molecular mechanism in tumorigenesis, present therapies are still limited for advanced tumors. Due to the limitation of current cancer treatment and side effects of chemotherapy, researchers attempt to search for new approach to control cancer development through cancer chemoprevention or by specific/multi-targets approach to improve efficiency of conventional therapies.

2.2 Cancer Chemoprevention and Treatment by Natural Compounds

Chemoprevention is the use of a chemical substance of either natural or synthetic origin to prevent, hamper, arrest, or reverse a disease. The term chemoprevention was coined by Sporn et al. (1976) in the mid-1970s. His work on retinoids against chemical carcinogenesis showed the time that cancer takes to develop in humans through the initiation, promotion, and progression stages. Cancer chemoprevention has a dual goal, i.e. prevention of occurrence of the disease (primary prevention) and early detection and reversion of tumors at a premalignant stage (secondary prevention). At a later stage, attempts can be made to prevent local recurrences as well as invasion and metastasis of malignant cells (tertiary prevention) (De et al. 2001; De and Ferguson 2005).

- Primary prevention: includes inhibition of mutation and cancer initiation, in the extracellular environment or inside cells, followed by inhibition of tumor promotion, such as, modifying transmembrane transport, modulating metabolism, blocking reactive species, detoxification, inhibiting cell replication, maintaining DNA structure, DNA repair, and controlling gene expression.
- Secondary prevention: exploits a variety of mechanisms aimed at inhibiting progression of a timely diagnosed benign tumor towards malignancy. It is possible to inhibit tumor progression *via* the same mechanisms, and in addition by affecting the hormonal status and the immune system in various ways, and by inhibiting angiogenesis and disruption of inflammatory microenvironment.
- Tertiary prevention: has the goal of preventing local relapses of the disease and of inhibiting invasion and metastasis or induction of programmed cell death in cancer cells.

Accumulated genetic alterations and dysregulated intracellular signaling are critical characteristics in cancer cells. Targeting on modulation of signaling molecules involved in tumorigenesis or leading to programmed cell death of cancer cells are promising approach in cancer therapy (Cho 2012). Both apoptosis and autophagy are types of programmed cell death that with entirely different mechanism and biological function (Edinger and Thompson 2004). Apoptosis is involving the concerted action of a number of intracellular signaling pathways, including members of the caspases family of cysteine proteases stored in most cells as zymogens or procaspases (Martin and Green 1995). Proteolytic cleavage of procaspases is an important step leading to caspase activation, which in turn is amplified by the cleavage and activation of other downstream caspases in the apoptosis cascade (Earnshaw et al. 1999; Stennicke and Salvesen 2000). The maintenance of homeostasis in normal mammalian tissues reflects a critical balance between cell proliferation and cell death *via* apoptosis. Induction of tumor cell apoptosis can be induced to augment interventions designed to suppress or reverse the development of cancer (Debatin 2004). Autophagy is defined as type 2 programmed cell death and is crucial for maintaining cellular homeostasis that responded to various microenvironment stresses, including starvation, pathogen infestation and chemotherapy (Cecconi and Levine 2008). It also functions as a backup when apoptosis is disabled (Maycotte and Thorburn 2011). However, the role of autophagy in cancer treatment is still controversial. Several reports exhibit that autophagy is a possible mechanism for tumor cell survival after cancer treatment (Hippert et al. 2006; Ravikumar et al. 2006; Degenhardt et al. 2006). Other studies reveal that autophagy induction appears to facilitate successful therapy-induced killing of tumor cells that suggesting a novel therapeutic strategy (Yang et al. 2011).

Over the past few decades, growing interesting in identify agents from natural sources which provide with preventing the initiation of tumors, arresting the development or metastasis of overt tumors and others (Yang et al. 2001). An effective and acceptable chemopreventive or anticancer agent should possess certain properties, include low cost, no toxic effects in normal and healthy cells, capability of oral consumption, high efficacy against multiple cancers, known mechanism of action, and acceptance by the human population (Galati and O'Brien 2004). Because of their pharmacological safety, most chemopreventive agents can be used in combination with chemotherapeutic agents to enhance the effect at lower doses and thus minimize chemotherapy-induced toxicity (Ferguson et al. 2005).

Many dietary phytochemicals such as curcumin, resveratrol, gingerols, sulforaphane and β-carotene have been shown to have cancer-preventing and therapeutic activities in laboratory studies (Pan and Ho 2008). As an example, tea and tea preparations have been shown to inhibit tumorigenesis in a variety of animal models of carcinogenesis, involving organ sites such as the skin, lungs, oral cavity, esophagus, stomach, liver, pancreas, small intestine, colon, and prostate (De and Ferguson 2005; Ferguson et al. 2005). The chemopreventive and chemotherapeutic mechanisms of natural dietary compounds are acting on regulation of redox status

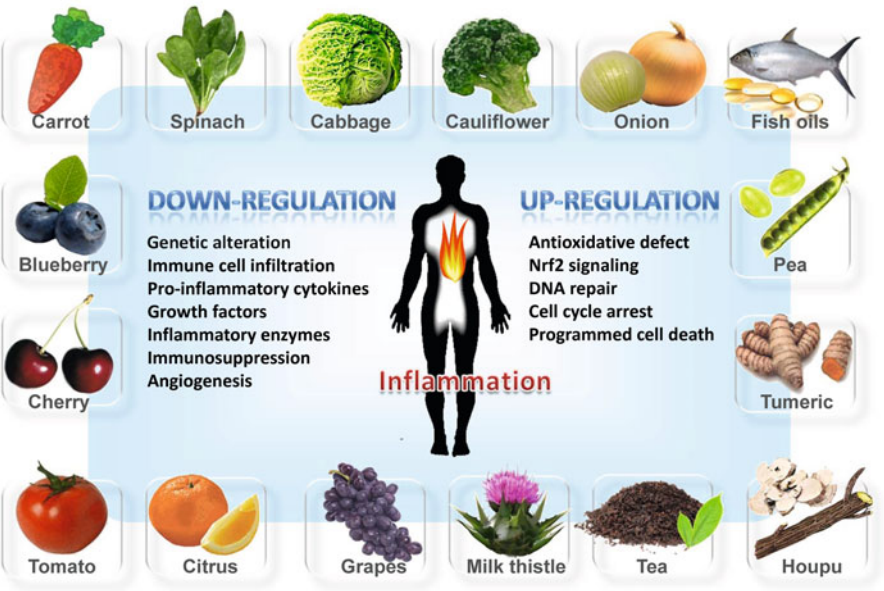


Fig. 2.2 Proposed mechanism of natural dietary compounds on cancer chemoprevention and chemotherapy

and signal transduction, modulation of gene expression involved in the suppression of inflammation, regulation of cell proliferation, differentiation, cell cycle and apoptosis and suppression of angiogenesis and metastasis, and thus inhibition of carcinogenesis (Pan and Ho 2008) (Fig. 2.2).

2.3 Chemopreventive and Chemotherapeutic Mechanisms of Flavonoids in Human Cancer

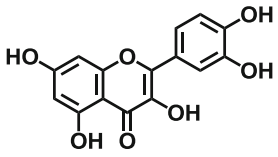
Numerous epidemiologic studies showed that the incidence of cancer is inversely correlated with the consumption of fruits and vegetables (Block et al. 1992; Vainio and Weiderpass 2006). Flavonoids are natural plant secondary metabolites in fruits, vegetables, nuts, seeds and plants and, with the burgeoning interest in alternative medicine, which increasingly been ingested by the general population. Chemically, flavonoids possess a basic 15-carbon skeleton and can be represented as C6-C3-C6 consisting of two benzene rings (C6) joined by a three carbon chain (C3). They can be classified by flavones, flavanones, flavonols, flavanonols, flavanols (catechins), anthocyanidins and isoflavones based on the differences in the structure of the aglycones C ring. The structural diversity of flavonoids is present in the pattern of basic structure such as hydroxylation and methoxylation, and the type of conjugation includes sulfonation, prenylation, or glycosylation, that display various biological activities (Beecher 2003).

Growing evidences exhibit a broad spectrum of pharmacological properties of flavonoids such as antioxidant, free radical-scavenging, anti-inflammatory, anti-carcinogenic, anti-viral, anti-bacterial, anti-thrombogenic and anti-atherogenic activities. It has been reported that human intake of all flavonoids is a few hundred milligrams to 650 mg/day in our diet (Liu 2004). Several researches indicate that dietary flavonoids may reduce cancer risk and display benefit for human health (Neuhouser 2004; Rossi et al. 2008; Graf et al. 2005). The chemopreventive and chemotherapeutic effects of flavonoids on various human cancers as well as their molecular mechanism are described below.

2.3.1 Flavonols (Table 2.1)

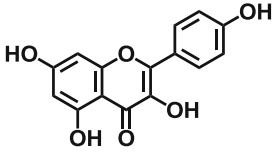
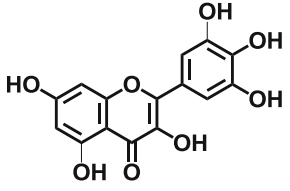
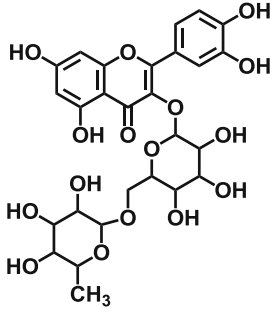
Quercetin is found typically in onions, broccoli, apples, grapes, wine, tea, and leafy green vegetables, and it is well known as a potent antioxidant and anti-inflammatory agent and effective in the prevention and modulation of different type of cancers. Dietary quercetin reduces azoxymethane (AOM)-induced aberrant crypt foci (ACF) formation by lowering crypt cell proliferation and increasing apoptosis in both F344 and SD rats (Warren et al. 2009; Turner et al. 2009). Decreased level of inflammatory enzyme cyclooxygenase-2 (COX-2) is also one of possible mechanisms for preventing colonic tumorigenesis in early stage (Turner et al. 2009). Quercetin is reported to inhibit the growth of colon cancer cells by induction of G2/M cell cycle arrest *via* downregulation of β-catenin/T cell factor (Tcf) transcriptional activity, thus decreasing gene expression of both *cyclin D1* and *survivin* that involved in cell cycle progression (Shan et al. 2009). Quercetin also induces apoptosis through targeting on epidermal growth factor receptor (EGFR) and AMP-activated protein kinase (AMPK) signaling in HT-29 colon cancer cells (Kim et al. 2005) and HT-29 xenograft tumor (Kim et al. 2010a), respectively. Moreover, quercetin enhances tumor radio-sensitivity in DLD-1 human colorectal cancer xenograft model through inhibiting Ataxia telangiectasia mutated (ATM) kinase that contributes to abate repair signaling in response to DNA damage (Lin et al. 2012a). Similar to the role of quercetin in colon cancer, it inhibits tumor growth by induction of apoptosis in human breast cancer MDA-MB-453 tumor growth *in vivo* (Dechsupa et al. 2007) and enhances radio-sensitivity in MCF-7 cancer cells (Lin et al. 2012a). In T98G and U87 glioblastoma cells, treatment with quercetin inhibits interleukin (IL)-6 triggered cell proliferation and migration through targeting on signal transducer and activator of transcription 3 (STAT3) and downstream target gene *cyclin D1* and matrix metalloproteinases (*MMP*)*-2* (Michaud-Levesque et al. 2012). In prostate cancer, quercetin causes endoplasmic reticulum (ER)-dependent apoptosis signaling in PC-3 cells and enhances eliminating prostate cancer stem cells (CSCs) characteristics by inhibition of self-renewal properties, and lowering vimentin, slug, snail levels involved in EMT, thus suppression of invasion and migration (Liu et al. 2012; Tang et al. 2010).

Table 2.1 Chemopreventive and chemotherapeutic effects of dietary flavonols on human cancers

Compound	Structure	Dietary source	Target cancer	Molecular mechanism	References
Quercetin		Broccoli, onion, apples and grapes	Colon cancer	Inhibits AOM-induced colorectal carcinogenesis by suppression of COX-2 expression, crypt cell proliferation and induction of apoptosis	Warren et al. (2009); Turner et al. (2009)
				Reduces β-catenin/T cell factor transcriptional activity, induces G2/M cell cycle arrest through decreasing gene expression of *cyclin D1* and *survivin* in SW480 colon cancer cells	Shan et al. (2009)
				Induces apoptosis *in vitro* and *in vivo* through targeting epidermal growth factor receptor and AMP-activated protein kinase signaling	Kim et al. (2005, 2010a)
				Enhances tumor radio-sensitivity in xenograft model through targeting ATM kinase	Lin et al. (2012a)
			Breast cancer	Induces apoptosis in human breast cancer MDA-MB-435 cells xenograft model	Dechsupa et al. (2007)
				Enhances radio-sensitivity *in vitro*	Lin et al. (2012a)
			Glioblastoma	Inhibits glioblastoma cells proliferation and migration by reduction of IL-6/signal transducer and activator of transcription 3 mediated *cyclin D1* and *MMP-2*	Michaud-Levesque et al. (2012)
			Prostate cancer	Induces apoptosis *via* ER-stress and mitochondrial signaling	Liu et al. (2012)
				Synergizes with EGCG in eliminating prostate cancer stem cells characteristics by inhibition of self-renewal properties, invasion and migration	Tang et al. (2010)
Kaempferol		Broccoli and tea	Colon cancer	Prevents 1,2-dimethyl hydrazine induced colonic tumorigenesis by reducing lipid peroxidation and increasing anti-oxidative enzymes in rats	Nirmala and Ramanathan (2011a)

(continued)

Table 2.1 (continued)

Compound	Structure	Dietary source	Target cancer	Molecular mechanism	References
			Ovarian cancer	Inhibits angiogenesis and tumor growth by decreasing vascular endothelial growth factor levels *via* hypoxia-inducible factor dependent and independent pathway	Luo et al. (2009)
				Induces apoptosis *via* activation of p53	Luo et al. (2011)
				Enhances chemotherapeutic effect by downregulation of c-myc in cisplatin-treated cells	Luo et al. (2010)
Myricetin		Grapes, berries and other fruits and vegetables	Pancreatic cancer	Induces apoptotic cell death *in vitro*, regresses tumor growth and reduces metastasis *in vivo*	Phillips et al. (2011)
			Bladder cancer	Induces G2/M cell cycle arrest and inhibits cell migration by targeting MMP-9 *in vitro*, reduces tumor growth in bladder cancer xenograft model	Sun et al. (2012)
			Colon cancer	Decreases 1,2-dimethylhydrazine-induced colonic tumorigenesis *via* upregulation of antioxidant levels and reduced lipid peroxidation	Nirmala and Ramanathan (2011b)
Rutin		Apple, orange, onion and citrus fruits	Leukemia	Synergistically inhibits vascular endothelial growth factor production with vitamin E by downregulating activator protein-1 and insulin receptor substrate 1 signaling	Chuang et al. (2010)
				Reduces tumor growth in leukemia xenograft model	Lin et al. (2012b)
				Reduces cell adhesion-mediated drug resistance by inducing apoptosis adherent leukemic progenitors *via* downregulation of active GSK3	Bourogaa et al. (2011)
			–	Protects benzo[*a*]pyrene-induced DNA damage in hepatoma tissue culture cells	Cristina et al. (2011)

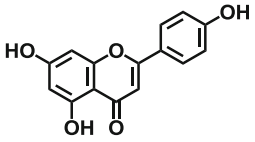
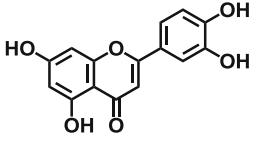
Kaempferol is another typical flavonol that commonly present in broccoli, tea and various vegetables. Study shows that dietary administration of 50–200 mg/kg kaempferol to rats causes significant upregulation of antioxidant enzymes including catalase, super oxide dismutase (SOD) and glutathione peroxidase (GPx) as well as decreasing lipid peroxidation that reduces 1,2-dimethyl hydrazine-induced colonic carcinoma in rats (Nirmala and Ramanathan 2011a). Several reports demonstrate the therapeutic effect of kaempferol in ovarian cancer. Kaempferol displays anti-angiogenic activity by inhibition of hypoxia-inducible factor (HIF)-dependent and independent vascular endothelial growth factor (VEGF) expression thus reduces tumor growth in human ovarian cancer cell lines and chorioallantoic membranes of chicken embryos model (Luo et al. 2009). Treatment with kaempferol induces apoptosis in ovarian cancer cells through p53-dependent mechanism (Luo et al. 2011). In addition, kaempferol sensitizes cisplatin-induced apoptosis by decreasing c-myc that contributes to overcome chemoresistance (Luo et al. 2010).

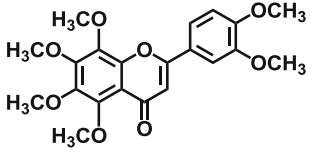
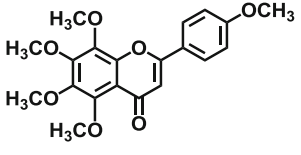
Myricetin, a naturally occurring flavonol in grapes, berries and other fruits and vegetables, has been found to possess anticancer property. In pancreatic cancer, myricetin induces apoptosis *in vitro*, regress tumor growth and decrease metastatic spreads in orthotopic pancreatic tumors through inhibition of phosphoinositide-3-kinase (PI3K) activity (Phillips et al. 2011). Myricetin also inhibits bladder cancer cells proliferation and migration by induction of G2/M phase cell cycle arrest and decreases of MMP-9 production that markedly reduces tumor growth in xenograft model (Sun et al. 2012). Consumption of myricetin at a dose of 50 and 100 mg/kg significantly suppress 1,2 dimethylhydrazine-induced colonic tumorigenesis through modulation of redox statue (Nirmala and Ramanathan 2011b). Rutin, also known as rutoside or sophorin, is a flavonol glycoside has a similar structure with quercetin that commonly present in apple, orange, onion and citrus fruits. Many studies have documented the potential of rutin on treatment of leukemia. In human promyelocytic leukemia (HL-60) cells, rutin and vitamin E synergistically inhibits VEGF secretion by suppression of activator protein-1 DNA-binding activity and interference with insulin receptor substrate-1 (IRS-1) signaling (Chuang et al. 2010). Treatment with rutin at a dose of 120 mg/kg inhibits tumor growth in a HL-60 xenograft animal model (Lin et al. 2012b). Rutin also displays a chemotherapeutic effect by induce apoptosis specifically in adherent leukemic cells thus contributes to abolish cell adhesion-mediated drug resistance (CAM-DR) (Bourogaa et al. 2011). Moreover, rutin is found to protect benzo[*a*]pyrene-induced DNA damage in hepatoma tissue culture (HTC) cells that may against carcinogen-induced toxic effect during metabolism (Cristina et al. 2011).

2.3.2 Flavones (Table 2.2)

Apigenin majorly presents in parsley and celery has been considered as an anticancer agent. Dietary apigenin (at a dose of 0.1 %) reduces AOM-induced ACF number by increasing colonocytes apoptosis in SD rats (Leonardi et al. 2010). In prostate

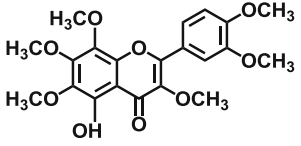
Table 2.2 Chemopreventive and chemotherapeutic effects of dietary flavones on human cancers

Compound	Structure	Dietary source	Target cancer	Molecular mechanism	References
Apigenin		Parsley and celery	Colon cancer	Reduces number of high multiplicity ACF and increases apoptosis in AOM-treated rats	Leonardi et al. (2010)
			Prostate cancer	Reduces prostate cancer cell motility and invasion by interfering with actin cytoskeleton and focal adhesion kinase/Src signalings	Franzen et al. (2009)
				Induces cell cycle arrest and apoptosis in prostate cancer cells and reduces tumor growth in xenograft model by inhibition of histone deacetylase	Pandey et al. (2012)
			Ovarian cancer	Sensitizes paclitaxel-induced apoptosis through accumulation of reactive oxygen species and activation of caspase-2 in ovarian cancer cells	Xu et al. (2011)
Luteolin		Beets, brussels sprouts and cabbage	Colon cancer	Prevents AOM-induced ACF formation by decreasing malondialdehyde-DNA adduct and increasing activities of antioxidant enzymes in mouse colon	Ashokkumar and Sudhandiran (2008)
				Decreases tumor incidence and size through interference with Wnt/β-catenin signaling and cyclin D1 levels in AOM-treated mice	Ashokkumar and Sudhandiran (2011)
			Lung cancer	Induces G2/M phase cell cycle arrest and apoptosis through inhibiting translocation of NF-κB	Cai et al. (2011)
				Inhibits cell invasion and growth of tumor xenografts in nude mice by targeting HDAC	Attoub et al. (2011)
				Inhibits hypoxia-induced epithelial mesenchymal transition by downregulation of integrin β1 and FAK	Ruan et al. (2012)

				Enhances tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis in lung cancer xenograft model	Yan et al. (2012)
			Liver injury	Reduces CCl_4-induced liver fibrosis by increasing MMP-9 and metallothionein I/II expression	Domitrovic et al. (2009)
				Protects D-galactosamine/lipopolysaccharide-induced liver injury by decreasing apoptosis and tumor necrosis factor-α release	Lee et al. (2011a)
Nobiletin		Citrus peel	Colon cancer	Reduces AOM and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine-induced ACF formation in mice	Suzuki et al. (2004); Tang et al. (2011)
				Reduces AOM and dextran sulfate sodium-induced tumor number partly through decreasing leptin in mice	Miyamoto et al. (2008)
			Prostate cancer	Inhibits PhIP-induced incidence and multiplicity of prostate adenocarcinomas by inhibiting cell proliferation	Tang et al. (2011)
			Gastric cancer	Suppresses cell invasion and migration through FAK/PI3K/Akt-mediated *MMP-2* and *MMP-9* gene expression and enzyme activity	Lee et al. (2011b)
Tangeretin			Lung cancer	Suppresses IL-1α-induced COX-2 expression *via* interfering with p38 mitogen-activated protein kinase, c-Jun N-terminal kinases and Akt signalings as well as downstream NF-κB activation	Chen et al. (2007)
			Ovarian cancer	Synergistically induces apoptosis and cell cycle arrest in cisplatin-resistant ovarian cancer cells through downregulation of PI3K/Akt signaling	Arafa et al. (2009)

(continued)

Table 2.2 (continued)

Compound	Structure	Dietary source	Target cancer	Molecular mechanism	References
			Colon and breast cancer	Inhibits cancer cell proliferation by induction of G1 cell cycle arrest	Morley et al. (2007)
5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone		Citrus peel	Leukemia	Induces apoptosis through ROS production and oxidative DNA damage	Pan et al. (2007)
			Colon cancer	Inhibits colony formation in various colon cancer cells by decreasing β-catenin and NF-κB	Qiu et al. (2011)
			Skin cancer	Inhibits 12-*O*-tetradecanoylphorbol-13-acetate-induced skin inflammation and tumor promotion by downregulation of inducible NO synthase and COX-2 *via* multiple signaling in mouse skin	Lai et al. (2007)

cancer cells, treatment with apigenin inhibits cell motility and invasion by alteration of cytoskeleton and accumulates focal adhesion proteins *via* decreased focal adhesion kinase (FAK)/Src signaling, thus promotes cell adhesion (Franzen et al. 2009). Otherwise, apigenin inhibits prostate tumor growth through epigenetic mechanism that evidenced by decreasing histone deacetylases (HDACs) activity that results in cell cycle arrest and apoptosis in nude mice (Pandey et al. 2012). Ovarian cancer cells treated with apigenin shows a synergistic effects in paclitaxel-induced apoptosis through increases of oxidative stress, indicating apigenin may act as a sensitizer with cancer therapy drugs (Xu et al. 2011).

Luteolin exists abundantly in thyme and also presents in beets, Brussels sprouts, cabbage and cauliflower that has been shown to possess chemopreventive and chemotherapeutic effects on various human cancers corresponding to its anti-oxidative, anti-proliferative, anti-invasion and apoptosis-inducing activity. In AOM-induced colon tumorigenesis model, orally treatment of luteolin at a dose of 1.2 mg/kg to rats reduces AOM-induced ACF formation through decreasing lipid peroxidation and increasing anti-oxidative enzyme activity that contributes to preventing malondialdehyde (MDA)-DNA adduct formation in rat colon (Ashokkumar and Sudhandiran 2008). In addition, luteolin decreases colonic tumor size by downregulation of Wnt/β-catenin signaling and downstream target gene *cyclin D1* expression (Ashokkumar and Sudhandiran 2011). A large body of studies demonstrates the effect of luteolin on lung cancer. Luteolin induces lung cancer cell apoptosis, cell cycle arrest, inhibits invasion and tumor growth *in vitro* and *in vivo* through multiple mechanisms, including downregulation of nuclear factor-κB (NF-κB) (Cai et al. 2011), decreasing HDACs activity (Attoub et al. 2011) and suppression of EMT (Ruan et al. 2012). Luteolin also enhances therapeutic efficacy in lung cancer xenograft model when it combines with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (Yan et al. 2012). It has been reported that the hepatoprotective property of luteolin is attributed to its ability on anti-fibrosis and reduction of hepatotoxicity induced by carbon tetrachloride (CCl_4) and D-galactosamine/lipopolysaccharide *in vivo* (Domitrovic et al. 2009; Lee et al. 2011a).

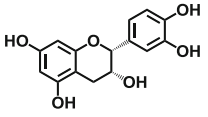
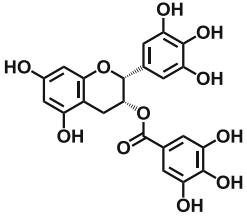
Nobiletin, tangeretin and 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone are polymethoxyflavones exist almost exclusively in citrus plants, particularly in citrus peel. Owning to the substituted methoxy groups, PMFs has a superior metabolic stability and membrane permeability over flavonoids (Wen and Walle 2006). Dietary feeding of nobiletin not only reduces ACF formation but also suppressed incidence and multiplicity of adenocarcinoma in AOM- and 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP)-treated animals (Suzuki et al. 2004; Tang et al. 2011). Nobiletin also completely abolished AOM/dextran sulfate sodium (DSS)-induced adenocarcinoma formation by reduction of leptin levels in ICR mice (Miyamoto et al. 2008). In PhIP-induced prostate cancer model, dietary feeding 0.05 % nobiletin significantly reduces number of prostate adenocarcinoma by suppression of cell proliferation (Tang et al. 2011). Nobiletin also displays anti-invasion activity in human gastric cancer cells by interfere with FAK and PI3K/AKT signaling and downstream target gene, *MMP-2* and *MMP-9* (Lee et al. 2011b).

Tangeretin exhibits anticancer property through modulation of intracellular signaling. Studies have supported the role of inflammation in the pathogenesis of lung cancer. Over-production of inflammatory mediators in lung cancer cells has been believed to implicate in tumor growth, invasion, migration and metastasis (Cho et al. 2011). Human lung carcinoma cells treated with tangeretin inhibits IL-1α-mediated NF-κB-dependent COX-2 expression *via* interference with multiple signaling molecules, such as p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinases (JNK) and Akt (Chen et al. 2007). In cisplatin-resistant human ovarian cancer cells, tangeretin synergistically induces apoptosis and cell cycle arrest with cisplatin by targeting PI3K/Akt signaling (Arafa et al. 2009). Tangeretin also inhibits human colon cancer and breast cancer cells proliferation through induction of G1 phase cell cycle arrest (Morley et al. 2007). 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone, a hydroxylated polymethoxyflavone, is particularly exists in the peels of sweet orange, has been reported to induce apoptosis in human leukemia cells and inhibit colony formation through downregulation of β-catenin and NF-κB in human colon cancer cells (Pan et al. 2007; Qiu et al. 2011). Topical application of 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone decreased expression levels of inducible NO synthase (iNOS) and COX-2, reduced nuclear translocation of NF-κB, and suppressed activation of extracellular regulated protein kinase (ERK) 1/2, p38 and AKT signaling in a 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-induced skin inflammation mouse model (Lai et al. 2007). Moreover, 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone inhibits 7,12-dimethylbenz[α]anthracene (DMBA)/TPA-induced skin tumor formation in mice. This study indicates that 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone is a potent chemopreventive agent.

2.3.3 Flavanols (Catechins) (Table 2.3)

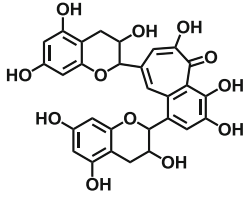
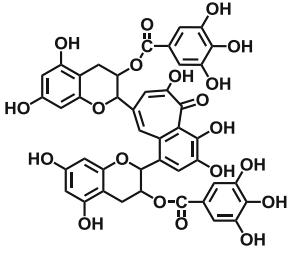
Tea is the most popular flavored and functional drink worldwide and possesses a broad spectrum of biological activities, including antioxidant, anti-carcinogenic, anti-inflammatory, anti-diabetic, anti-hyperlipidemia and anti-obesity. Green and black tea is account for about 20 and 78 % worldwide tea consumption, respectively. Nemours studies have demonstrated the potential of green tea and black tea on cancer chemoprevention, including colon cancer, prostate cancer, ovarian cancer and rectal cancer are attributing to their polyphenolic compounds, catechins and theaflavins (Yang et al. 2007; Yuan et al. 2011; Baker et al. 2007; Dora et al. 2003). In rats with acute myeloid leukemia, (−)-epicatechin (EC) is found to induce apoptosis of leukemia cells in the spleen but without cause toxic effect in splenocytes that may against acute myeloid leukemia (Papiez et al. 2010). When combine with curcumin, EC enhances growth inhibitory effect and induction of apoptosis in human lung cancer cell line (Saha et al. 2010). *In vivo* study also demonstrates that the combination of EC with vitamin E effectively protects nicotine-induced oxidative damage in rats (Al-Malki and Moselhy 2013). (−)-Epigallocatechin-3-gallate (EGCG), the most abundant catechin in green tea,

Table 2.3 Chemopreventive and chemotherapeutic effects of dietary flavanols (catechins) on human cancers

Compound	Structure	Dietary source	Target cancer	Molecular mechanism	References
(−)-Epicatechin		Tea	Leukemia	Induces apoptosis of leukemia cells in the spleen in leukemic rats	Papiez et al. (2010)
			Lung cancer	Enhances growth inhibitory and apoptotic effect with curcumin by upregulation of growth arrest and DNA damage induced gene (*GADD*)*153* and *GADD45*	Saha et al. (2010)
				Enhances protective effect on against nicotine-induced oxidative stress with vitamin E by upregulation of antioxidants in rat	Al-Malki and Moselhy (2013)
(−)-Epigallocatechin-3-gallate		Tea	Melanoma	Inhibits cell invasion and migration through targeting PGE receptors/COX-2/ prostaglandin E_2 and EMT	Singh and Katiyar (2011)
			Colon cancer	Inhibits colorectal ACF formation by interfere with IGF/ IGF-IR and β-catenin signaling in AOM-induced colonic carcinogenesis model	Shimizu et al. (2008)
			Liver cancer	Protects CCl_4-induced liver fibrosis through reducing oxidative stress, collagen accumulation and inflammatory mediators production	Tipoe et al. (2010)
			Skin cancer	Reactivation of tumor suppressor genes through inhibiting DNA methyltransferases and decreasing HDAC activity	Nandakumar et al. (2011)
			Breast cancer	Inhibits nicotine and estrogen-induced cell proliferation through downregulation of 9-α nicotinic acetylcholine receptor	Tu et al. (2011)
			Lung cancer	Inhibits cell invasion and migration through downregulating JNK-dependent MMP-2 expression	Deng and Lin (2011)
			Gastric cancer		Wu et al. (2012)

(continued)

Table 2.3 (continued)

Compound	Structure	Dietary source	Target cancer	Molecular mechanism	References
				Enhances docetaxel-induced gastric tumor growth inhibition by suppression of angiogenesis in xenograft model	
Theaflavin		Black tea	Breast cancer	Induces apoptosis through death receptor cascade and inhibits pAkt/pBad survival pathway in p53-mutated human breast cancer cells	Lahiry et al. (2010)
				Inhibits fatty acid synthase level in MCF-7 breast cancer cells	Yeh et al. (2003)
			Lung cancer	Against benzo[*a*]pyrene-induced lung carcinogenesis through induction of apoptosis and inhibition of COX-2 expression in mice	Banerjee et al. (2005, 2006)
				Inhibits bronchiolar cell proliferation and tumor formation in 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung carcinogenesis in A/J mice	Yang et al. (1997)
			Melanoma	Induction of apoptosis through increasing ROS production and activation of JNK-p38 MAPK signaling	Bhattacharya et al. (2009)
				Suppression of *MMP-2* gene expression and activity by downregulation of EGFR and NF-κB signaling	Sil et al. (2010)
Theaflavin-3,3′-digallate (TF-3)		Black tea	Oral cancer	Induced apoptosis by increasing oxidative stress in human oral squamous cells	Schuck et al. (2008)
			Lung cancer	Induces cell cycle arrest combined with ascorbic acid in human lung adenocarcinoma cells	Li et al. (2010)

has been considered as a promising chemopreventive and anticancer agent. EGCG inhibits human melanoma cells invasion and migration which is associate with suppression of transition of mesenchymal stage to epithelial stage and endogenous expression of COX-2 and prostaglandin E_2 (PGE_2) (Singh and Katiyar 2011). Supplementation with 0.01 and 0.1 % EGCG in drinking water suppresses AOM-induced ACF formation by downregulation of insulin-like growth factor (IGF), β-catenin and downstream gene *cyclin D1* and *COX-2* in C57BL/KsJ-db/db mice (Shimizu et al. 2008). EGCG also displays hepatoprotective and anti-fibrosis effect evidenced by reduction of oxidative stress, collagen accumulation and inflammatory mediators production including tumor necrosis factor (TNF)-α, COX-2 and iNOS (Tipoe et al. 2010). In human skin cancer cells, EGCG function as an epigenetic regulator that reactivation of tumor suppressor genes, *Cip1*/*p21* and *p16INK4a*, *via* reduction of DNA methylation and increases of histone acetylation (Nandakumar et al. 2011). Human breast cancer cells treated with EGCG inhibits nicotine-induced proliferation by targeting on α9-α nicotinic acetylcholine receptor (nAChR) signaling pathway (Tu et al. 2011). Additionally, EGCG shows anti-invasion and anti-migration activity in invasive human lung cancer cells by induction of G2/M phase cell cycle arrest and JNK-dependent MMP-2 expression (Deng and Lin 2011). When combination with chemotherapeutic drug, docetaxel, EGCG demonstrates an enhanced effect on suppression of gastric xenograft tumor growth by decreasing tumor angiogenesis *in vivo* (Wu et al. 2012).

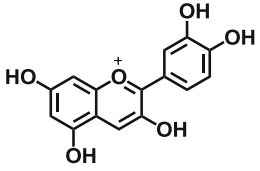
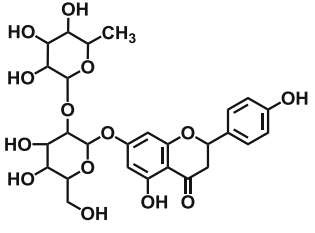
Theaflavins include theaflavin (TF1), theaflavin-3-*O*-gallate (TF2a), theaflavin-3′-*O*-gallate (TF2b) and theaflavin-3,3′-*O*,*O*-digallate (TF3) are major polyphenolic compounds in black tea. The anti-proliferative and apoptosis-inducing activity of TF1 has been documented in various cancer cell lines. Treatment with TF1 results in induction of death receptor/caspase-8 dependent apoptosis and inhibits pAkt/pBad survival signaling in p53-mutated human breast cancer cells that may reduce drug-resistance (Lahiry et al. 2010). TF1 also downregulates fatty acid synthase in human breast cancer MCF-7 cells that may contributes to reduce cell lipogenesis and proliferation (Yeh et al. 2003). Dietary TF-1 has been shown to against lung cancer in different animal model. Consumption of TF-1 prevents benzo [*a*]pyrene (BP)-induced lung carcinogenesis through induction of apoptosis and inhibition of COX-2 expression *in vivo* (Banerjee et al. 2005, 2006). Moreover, administration of TF-1 in drinking water reduces NNK-induced lung carcinogenesis caused in A/J mice (Yang et al. 1997). In human melanoma cell line, treatment with TF1 induces apoptosis *via* ROS generation and MAPKs signaling (Bhattacharya et al. 2009). Also, TF1 may against melanoma cell invasion by suppression of MMP-2 *via* downregulation of epidermal growth factor receptor (EGFR), ERK and NF-κB signaling (Sil et al. 2010). TF3, another theaflavin in black tea, is found to induce apoptosis *via* increased oxidative stress in human oral squamous cells (Schuck et al. 2008). TF3 also reveals synergistic effect on induction of cell cycle arrest when combined with ascorbic acid in human lung adenocarcinoma cells (Li et al. 2010).

2.3.4 *Flavonones (Table 2.4)*

Dietary consumption of 0.02 % naringenin, a naturally occurring citrus flavonone, has been found to suppress AOM-induced colonic ACF formation by decreasing cell proliferation and promoting apoptosis in colonocytes (Leonardi et al. 2010). Naringenin may be considered as immunomodulator supported by significantly reducing lung metastases in mice with pulmonary fibrosis through downregulation of transforming growth factor (TGF)-α1 and reducing regulatory T cells that involved in creation of immunosuppressive environment within tumor tissue (Du et al. 2009). Administration of naringenin reduces tumor growth by modulation of redox statue that against *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine-induced gastric carcinogenesis in rats (Ekambaram et al. 2008). In cerebrally implanted C6 glioma cells rat model, naringenin is found to increase expression of connexin 43 (Cx43), a molecule involved in gap junction, thus promotes apoptosis of glioma cells (Sabarinathan et al. 2010). Naringenin also has been reported to protect against UVB-induced DNA damage by accelerating of cyclobutane pyrimidine dimers (CPD) removal and decreasing apoptosis in human keratinocytes HaCaT cells (El-Mahdy et al. 2008). Naringin is another flavonone naturally occurs in citrus. Administration of naringin at a dose of 25 mg/kg is effective on reducing tumor growth by downregulation of inflammatory cytokines TNF-α and IL-6 in rats with Walker 256 carcinosarcoma (Camargo et al. 2012). Naringin also demonstrates protective property against carcinogen-induced lung injury by increasing antioxidant, downregulation of inflammatory cytokine production and suppression of neutrophil infiltration in cigarette smoke (CS) and lipopolysaccharides (LPS)-treated animal models (Luo et al. 2012; Liu et al. 2011).

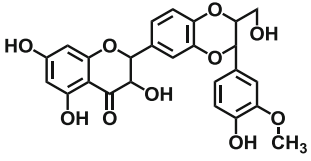
Silibinin is the major flavonolignan isolated from seed of milk thistle (*Silybum marianum*), has been believed to possess anticancer efficacy and liver protective effect with its mixture form, similarly. Dietary 0.5 % silibinin induces apoptosis and inhibits angiogenesis *via* downregulation of Bcl-2, survivin and VEGF expression, thus suppresses prostate tumor growth in nude mice (Singh et al. 2007). In metastatic prostate cancer cells, silibinin causes suppression of invasive property by reversing EMT *via* targeting on NF-κB, vimentin and MMP2 (Wu et al. 2010). Silibinin treatment induces apoptosis in human bladder cancer cells and bladder xenograft tumor growth through interfering with STAT3 signaling, and caspase- dependent and -independent pathway (Agarwal et al. 2007; Zeng et al. 2011). Orally feeding silibinin at a dose of 750 mg/kg suppressed colonic tumorigenesis through inhibition of cell proliferation (β-catenin, cyclin D1), inflammation (iNOS, COX-2), angiogenesis (VEGF) and induction of apoptosis in AOM-treated A/J mice and $APC^{min/+}$ mice (Ravichandran et al. 2010; Rajamanickam et al. 2010). In addition, silibinin displays anti-metastatic property evidenced by inhibition of migration and adhesion *via* decreasing cell division control protein 42 (Cdc42) and D4-GDI (a Rho GTPases regulator) that may prevent metastasis of human highly metastatic breast cancer cell to distant organs (Dastpeyman et al. 2011). In human cervical cancer cell line, silibinin treatment induces both apoptosis and autophagy by increasing of oxidative stress including ROS and reactive nitrogen species (RNS) (Fan et al. 2011).

Table 2.4 Chemopreventive and chemotherapeutic effects of dietary flavanones on human cancers

Compound	Structure	Dietary source	Target cancer	Molecular mechanism	References
Naringenin		Orange peel	Colon cancer	Suppresses AOM-induced ACF formation by inhibiting colonocyte proliferation and increasing apoptosis	Leonardi et al. (2010)
			Lung cancer	Reduces lung metastases in mice with pulmonary fibrosis by downregulation of TGF-α1 and regulator T cells	Du et al. (2009)
			Gastric cancer	Reduces *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine-induced gastric carcinogenesis by upregulation of redox status	Ekambaram et al. (2008)
			Glioma	Promotes apoptosis through mitochondrial pathway and Cx43 in cerebrally implanted C6 glioma cells rat model	Sabarinathan et al. (2010)
			Skin cancer	Protects UVB-induced DNA damage by removal of cyclobutane pyrimidine dimers and apoptosis in human keratinocytes	El-Mahdy et al. (2008)
Naringin			Carcinosarcoma	Reduces tumor growth by decreasing TNF-α and IL-6 levels *in vivo*	Camargo et al. (2012)
			Lung cancer	Inhibits cigarette smoke exposure-induced chronic bronchitis by reducing inflammatory cytokines production and increasing SOD activity	Luo et al. (2012)
				Reduces lipopolysaccharides-induced lung injury and edema by decreasing neutrophil infiltration and TNF-α secretion *via*	Liu et al. (2011)

(continued)

Table 2.4 (continued)

Compound	Structure	Dietary source	Target cancer	Molecular mechanism	References
				interference with NF-κB	
Silibinin		Milk thistle	Prostate cancer	Suppresses prostate xenographic tumor growth by induction of apoptosis and inhibition of angiogenesis	Singh et al. (2007)
				Reduces invasive property of metastatic prostate cancer cells by alteration of EMT *via* targeting NF-κB	Wu et al. (2010)
			Bladder cancer	Inhibits activation of STAT3 in DU145 cancer cells and inhibits bladder xenograft tumor growth through induction of caspase-dependent and -independent apoptosis	Agarwal et al. (2007); Zeng et al. (2011)
			Colon cancer	Inhibits colonic tumorigenesis through downregulation of inflammatory and angiogenic molecules and induction of apoptosis in AOM-treated and $APC^{min/+}$ mice	Ravichandran et al. (2010); Rajamanickam et al. (2010)
			Breast cancer	Inhibits cell migration and adhesion by decreasing cell division control protein 42 and D4-GDI levels	Dastpeyman et al. (2011)
			Cervical cancer	Induces apoptosis and autophagy by increasing ROS and reactive nitrogen species	Fan et al. (2011)

2.3.5 *Anthocyanidins (Table 2.5)*

Anthocyanidins are water-soluble glycosides and common plant pigments that give the red and blue colors in many cereal grains, and flowers, fruits and vegetables such as blueberries and grapes. Cyanidin is reported to synergistic against H_2O_2-induced cytotoxicity with peroxisome proliferator-activated receptors (PPAR) agonist through decreasing oxidative stress *via* activation of NF-E2-related factor 2 (Nrf2), an important transcription factor of antioxidant enzymes (Shih et al. 2012). Cyanidin also reduces UVB-induced COX-2 expression through targeting multiple signalings, such as MKK4, MAP kinase (MEK1) and Raf-1 in epidermal cells that contributes to suppression of UVB-induced inflammatory response in skin (Kim et al. 2010b). Cyanidin-3-glucoside, another natural colorant found in bilberries and other fruits, is shown to scavenge UVB-induced free radicals, block TPA-induced neoplastic transformation in epidermal cells, and decrease tumor number in DMBA/TPA skin tumorigenesis model *via* downregulation of COX-2 and TNF-α production (Ding et al. 2006). In *in vitro* and *in vivo* study, cyanidin-3-glucoside effectively suppresses lung cancer cell proliferation and metastasis by reduction of invasion and migration *via* decreasing MMP-2 level (Chen et al. 2006; Ding et al. 2006).

Delphinidin also shows chemoprotective and anticancer effects against prostate, breast and liver cancer. Studies show that delphinidin modulates NF-κB signaling that induces apoptosis, cell cycle arrest and inhibits prostate tumor growth *in vitro* and *in vivo* (Bin et al. 2008; Hafeez et al. 2008). In human breast cancer cells, treatment of delphinidin causes apoptosis through decreasing HER2 and ERK1/2 signalings (Ozbay and Nahta 2011). Administration with delphinidin inhibits CCl_4-indcued oxidative stress, reduces collagen accumulation, inactivates hepatic stellate cells (HSC) and restores hepatic injury that contribute to reduce liver fibrosis (Domitrovic and Jakovac 2010).

2.3.6 *Isoflavones (Table 2.6)*

Isoflavones are usually recognized as phytoestrogen compounds which rich in soybeans. Many studies have revealed the health benefits of soybeans are derived from isoflavones, such as anti-atherosclerotic and anticancer. Genistein and daidzein are major isoflavones that abundantly present in soybeans, possess chemopreventive and anticancer activity evidenced by numerous *in vitro* and *in vivo* studies. In human ovarian cancer cells, treatment of genistein induces both apoptosis and autophagy as well as decreases glucose uptake *via* downregulation of Akt that may contribute towards a mechanism to limit glucose utilization (Gossner et al. 2007). Genistein is effective on drug-resistant ovarian cancer by sensitizing cisplatin-induced apoptosis *via* targeting on NF-κB (Solomon et al. 2008). Dietary genistein displays protective effect against 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced chronic colitis *via*

Table 2.5 Chemopreventive and chemotherapeutic effects of dietary anthocyanidins on human cancers

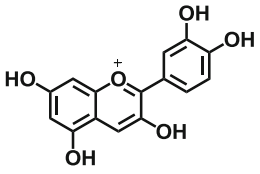
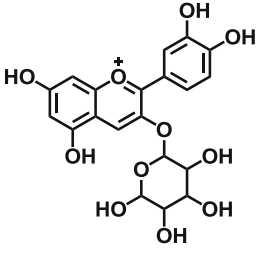
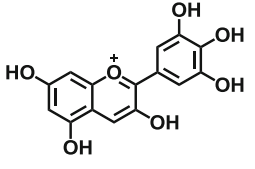
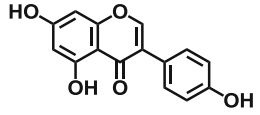
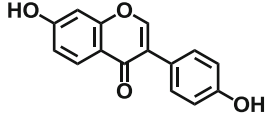
Compound	Structure	Dietary source	Target cancer	Molecular mechanism	References
Cyanidin		Cherries and strawberries	Liver cancer	Synergistic against nonalcoholic steatohepatitis-induced oxidative stress and cytotoxicity with peroxisome proliferator-activated receptors agonist through activation of NRF-2	Shih et al. (2012)
			Skin cancer	Suppresses UVB-induced COX-2 expression through interfere with MKK4, MAP kinase and Raf-1 activity	Kim et al. (2010b)
Cyanidin-3-glucoside		Blackberry	Skin cancer	Scavenges UVB-induced free radicals, inhibits TPA triggered neoplastic transformation and suppresses DMBA/TPA-induced skin tumor by decreasing inflammatory mediators production	Ding et al. (2006)
			Lung cancer	Inhibits lung cancer cell proliferation and metastasis in xenograft model by suppression of migration and invasion	Ding et al. (2006)
				Inhibits lung cancer cell migration and invasion by downregulation of MMP-2 and urokinase-plasminogen activator	Chen et al. (2006)
Delphinidin		Dark fruits and vegetables	Prostate cancer	Induces apoptosis, cell cycle arrest and inhibits tumor growth through interfere with NF-κB signaling *in vitro* and *in vivo*	Hafeez et al. (2008); Bin et al. (2008)
			Breast cancer	Induces apoptosis through inhibition of HER2 and ERK1/2 signaling	Ozbay and Nahta (2011)
			Liver cancer	Against CCl_4-induced liver fibrosis through decreasing oxidative stress, promoting extracellular matrix degradation and inactivation of hepatic stellate cells	Domitrovic and Jakovac (2010)

Table 2.6 Chemopreventive and chemotherapeutic effects of dietary isoflavones on human cancers

Compound	Structure	Dietary source	Target cancer	Molecular mechanism	References
Genistein		Soybean	Ovarian cancer	Induces autophagy and inhibits glucose uptake through downregulation of Akt	Gossner et al. (2007)
				Sensitizes cisplatin-induced cytotoxicity through induction of apoptosis and inhibition of NF-κB	Solomon et al. (2008)
			Colon cancer	Reduces 2,4,6-trinitrobenzenesulfonic acid-induced chronic colitis by decreasing COX-2 levels and myeloperoxidase activity	Seibel et al. (2009)
				Synergistic induces apoptosis with indol-3-carbinol through inhibition of Akt	Nakamura et al. (2009)
			Prostate cancer	Inhibits lung micrometastasis by increasing adhesion *via* upregulation of promotility proteins in nude mice	Lakshman et al. (2008)
				Reduces *N*-methylnitrosourea-induced advanced prostate cancer by increasing apoptosis and inhibiting proliferation *via* Akt/ phosphatase and tensin homolog signaling	Wang et al. (2009)
				Reduces COX-2 and PGE_2 levels in prostate cancer patients	Swami et al. (2009)
Daidzein		Soybean	Glioma	Enhances therapeutic effect with TRAIL by increasing apoptosis *via* downregulation of Bcl2 in chemoresistance glioma cells	Siegelin et al. (2009)
			Breast cancer	Inhibits proliferation by inducing G1 and G2/M cell cycle arrest	Choi and Kim (2008)
			Skin cancer	Synergistically protects UVB-induced DNA damage and reducing COX-2 levels with genistein	Iovine et al. (2011)
			Liver cancer	Against DMBA-induced oxidative stress *via* increasing antioxidant status and reduction of hepatocyte apoptosis in liver	Choi and Kim (2009)

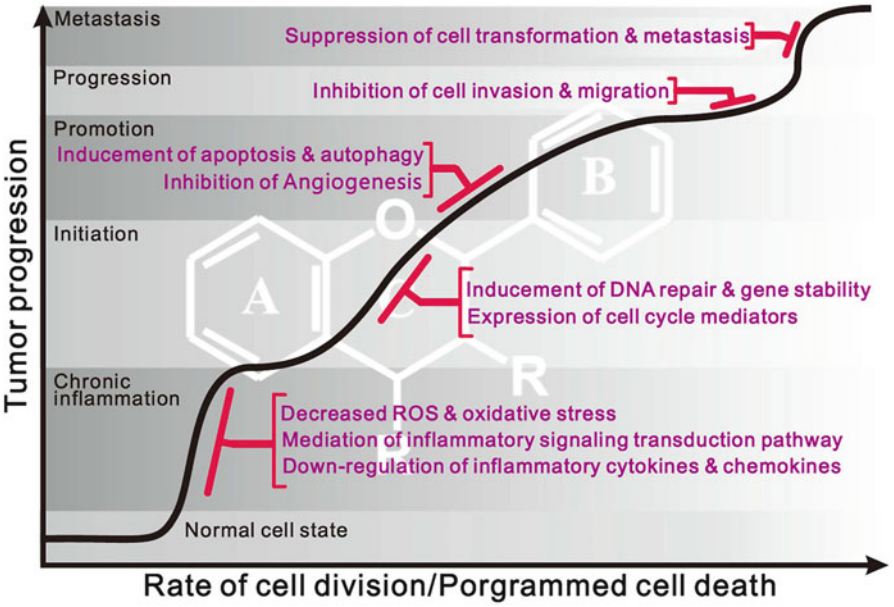


Fig. 2.3 Proposed mechanism of flavonoids from fruits and vegetables on cancer chemoprevention and chemotherapy

anti-inflammatory mechanism, including reduction of COX-2 expression and myeloperoxidase (MPO) activity (Seibel et al. 2009). In combination with indole-3-carbinol, a breakdown product of the glucobrassicin which can be found at relatively high levels in cruciferous vegetables, synergistically induces apoptosis through interfere with Akt in human colon cancer cells (Nakamura et al. 2009). Several studies demonstrate the potential of genistein against prostate cancer. Dietary genistein effectively inhibits lung micrometastasis of orthotopically implanted human prostate cancer cells by increasing promotility proteins that contributes to increase adhesion property of cancer cells (Lakshman et al. 2008). Genistein also reduces *N*-methylnitrosourea (NMU)-induced advanced prostate cancer *in vivo* through targeting on phosphatase and tensin homolog, known as a tumor suppressor, and Akt signaling, thus suppression of cell proliferation and increase of apoptosis (Wang et al. 2009). In prostate cancer patients, supplement with genistein significant decreases prostate COX-2/PGE_2 levels that may beneficial to the treatment prostate cancer (Swami et al. 2009).

Daidzein, another isoflavone exists in soybeans, is found as chemotherapy sensitizer supported by enhancement of TRAIL-induced apoptosis in chemoresistance glioma cells (Siegelin et al. 2009). Treatment of daidzein causes cell proliferation inhibition through induction of G1 and G2/M phase cell cycle arrest in different human breast cancer cells (Choi and Kim 2008). Additionally, combination of daidzein and genistein shows a synergistically protective effect against UVB-induced DNA damage and decreasing COX-2 levels in human fibroblasts, indicating a

protective role for UVB-induced skin damage and inflammation (Iovine et al. 2011). Orally feeding daidzein (5 and 25 mg/kg) displays hepatoprotective efficacy against DMBA-induced oxidative stress, increasing antioxidant statue (glutathione peroxidase and reductase) and reducing hepatocytes apoptosis in mouse liver (Choi and Kim 2009).

2.4 Conclusions and Perspectives

Cancer is the major challenge to human health. In concept of overcome this challenge, there is needed new approach to control cancer development through cancer chemoprevention or chemotherapy by specific/multi-targets to improve efficiency of conventional therapies. Natural compounds from diet are now considered to offer great potential in the prevention and management of cancer. Flavonoids are widely present in vegetables, fruits and edible plants that display great cancer chemopreventive and chemotherapeutic effects on various human cancers. Their possible mechanism includes interference in several of the steps that lead to the development of malignant tumors, such as protecting DNA from oxidative damage, inhibiting carcinogen activation, and activating carcinogen detoxifying systems (Fig. 2.3). They also inhibit the promotion stage of carcinogenesis by inhibiting oxygen radical-forming enzymes or enzymes that contribute to DNA synthesis or acts on inhibition of signaling molecules that contribute to proliferation, inflammation, EMT, angiogenesis, invasion and migration. Finally, they may prevent tumor development by inducing programmed cell death of tumor cell including apoptosis and autophagy as well as trigger cell cycle arrest.

Despite a number of studies have addressed the anticancer effect of flavonoids from fruits and vegetables, little is known about the mechanism of action of most compounds. Flavonoids can directly and indirectly influence cancer development likely to be an integrated effect of several distinct mechanisms. Therefore, identify specific targets and understanding of the critical events associated with tumorigenesis would provide the better investigation of their underlying mechanism. In addition, many *in vitro* and *in vivo* researches have reported the effects of flavonoids on various human cancers, but not final conclusion. In cell culture system and animal study, the dosage of flavonoids may not be attained in our regular diet. Although several epidemiological research report the efficacy of dietary flavonoids on against human cancer, but some are still contradictory. Before application of general public, well-designed and carefully clinical studies should be evaluated in intervention trials for potential of flavonoids as cancer chemopreventive agents. Moreover, the absorption, bioavailability, metabolism and pharmacokinetic properties are important issues for dietary intervention of flavonoids on human cancers. In fact, the structure and functional group of some flavonoids might limit their oral bioavailability. Poor absorption and extensive conjugative metabolisms in the intestine and liver greatly limit bioavailability of dietary flavonoids. Constructing an appropriate vehicle and the desired efficient formulation possess a challenge to dietary supplement

researchers. It is also possible that these dietary flavonoids can be used as sensitizers to enhance the efficacy of other known chemotherapeutic agent that offer effective approach on malignant or chemoresistance cancers. Further mechanistic insights are needed to elucidate for dietary flavonoids on cancer chemoprevention and treatment that should provide innovative approaches for control of cancers.

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