Cancer Chemoprevention by Dietary Polyphenols, Flavonoids, Terpenoids, and Saponins

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Abstract

Cancer chemoprevention invokes the adoption of natural or man-made agents for the inhibition, delay, or reversal of carcinogenesis before an invasion. It is predicted that roughly one-third of all cancer deaths might be prevented through proper dietary alteration. Chemopreventives should be defined by low toxicity in therapeutic drugs and the possibility of an oral administration. Several epidemiological studies and preclinical evidence indicate that various nutraceuticals and dietary supplements display chemopreventive properties, which is well supported by in vitro and animal studies. Diet derived compounds widely investigated for their chemopreventive activity mostly belong to a class of polyphenols, flavonoids, terpenoids, or saponins. A well-balanced diet is an excellent source of macronutrients, micronutrients, and phytochemicals and can diminish the risk of cancer as well as provide cancer preventive activity.

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Dietary phytochemicals · Cancer · Chemoprevention · Epidemiology · Epigenetics · Apoptosis

5.1 Cancer Chemoprevention by the Dietary Phytochemicals

Cancer ranks as one of the top leading causes of morbidity and mortality worldwide, with roughly 18.1 million new cancer cases and 9.6 million cancer deaths in 2018. It is also expected that the number of cases will increase by about 70% over the ensuing two decades reaching 22 million annual cases (Bray et al. 2018; McGuire 2016). Carcinogenesis is a mechanism by which a normal cell is transformed into a cancer cell. This is due to the mutation and epimutation of the genetic material of normal cells, which agitates the harmony between proliferation and apoptotic cell death. This causes uncontrolled cell proliferation and the formation of cancer. Chemoprevention is action taken to thoroughly cut-off or lower the chance of getting cancer by actively intervening in the course of carcinogenesis (Zhang et al. 2017; Al Rabadi and Bergan 2017). Scientists are investigating many different ways to support the prevention of cancer, including the following:

- Avoiding or controlling cancer causing things.
- Managing changes in diet and lifestyle.
- Early detection of precancerous conditions that may lead to cancer.
- Chemoprevention (medicine to stop or reduce cancer conditions from the initial stage).
- Risk-reducing surgery.

An abundance of data suggests that lifestyle factors, along with exposure to chemical carcinogens, diet, and lack of physical activity play a pivotal role in the advancement of common cancers. It has been predicted that appropriate lifestyle modifications could prevent more than two-thirds of human cancers.

Diet is closely linked to the incidence and prevention of different cancer types and dietary behavior has been diagnosed as one of the most significant modifiable lifestyle impetus of cancer risk. Human cancer deaths attributable to diet make up nearly 10–70% (average 35%). Therefore diet, together with a healthy lifestyle, can reduce cancer incidence by 30–40%. In fact, most authors agree that there is consistent epidemiological evidence to suggest that a diet rich in fruits or vegetables significantly rolls back the risk of certain disorders, such as cancer and cardiovascular diseases (De Stefani et al. 2000).

In consequence, several international organizations, like the World Cancer Research Fund (WCRF), American Institute for Cancer Research (AICR), and other various cancer research foundations, endorsed a boost in the ingestion of certain fruits, vegetables, and grains as their incorporation in diet is associated with a reduced risk for the spreading of certain tumors and cancers (Mosby et al. 2012; Gapstur et al.

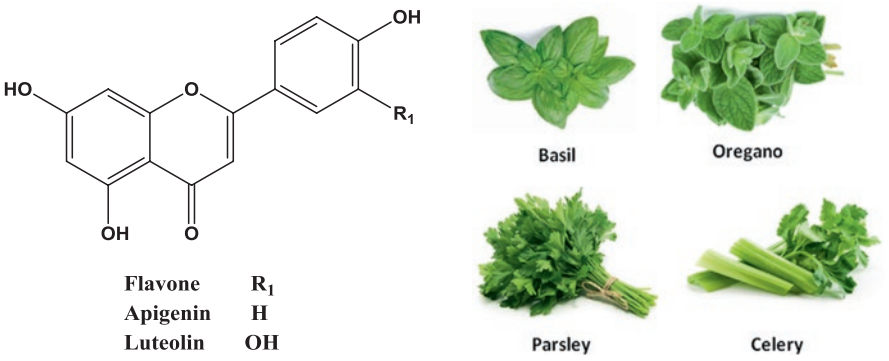
2018). The National Cancer Institute (NCI) has picked out about 35 plant-based foods with cancer-preventive properties. Foods and herbs possessing these qualities include garlic, cabbage, soybeans, licorice root, ginger, and the umbelliferous vegetables (including celery, carrots, coriander, parsnips, and parsley). Additional foods with anticancer activity include citrus, onions, flax, turmeric, cruciferous vegetables (Brussels sprouts, broccoli, cabbage, and cauliflower), sweet peppers and tomatoes, brown rice, oats, barley, whole wheat, various herbs, such as rosemary, mints, thyme, sage, oregano, and basil, cantaloupe, cucumber, and berries (Wiseman 2018; Surh 2003). Plenty of secondary plant products, such as polyphenols (Thomasset et al. 2007), terpenoids (Rabi and Gupta 2008), saponins (Raju and Mehta 2009), flavonoids (Galati and O'Brien 2004), carotenoids (Tanaka et al. 2012). etc., which are substantial constituents of our daily food, have thus transformed themselves from being considered as non-nutritive constituents to possibly cancer preventive ones.

5.2 Occurrence of Polyphenols, Flavonoids, Terpenoids, and Saponins in Diet

Dietary phytochemicals are divided into four main classes according to their chemical structures: polyphenols, terpenoids, alkaloids, and sulfur compounds. Among them, dietary polyphenols and flavonoids are the rich antioxidants in human diets (Table 5.1). They are further subdivided into groups based on the number of

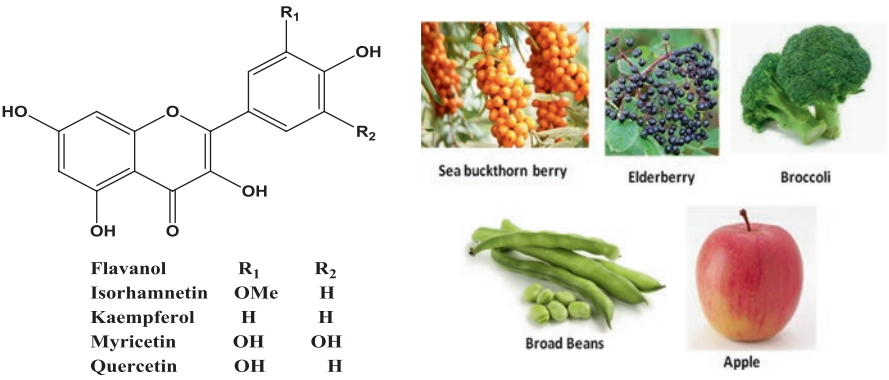
Table 5.1 Dietary sources of polyphenols

Subclass	Compounds	Primary source
Flavonols	Quercetin, myricetin, kaempferol, rutin, isorhamnetin	Vegetables: capers, chives, celery, onions, red onions, lettuce, dock leaves, broccoli, hartwort leaves, kale
		Fruits: apricots, apples, grapes, plums, bilberries, blueberries, blackberries, cranberries, olive elderberries, black currant juice, currants, cherries, apple juice
		Drink: red wine, tea (green and black)
Flavanones	Hesperin, hesperidin, naringin, eriodictyol, naringenin	Citrus fruits and juices: orange, orange juice, lemon, lemon juice, lime juice, grapefruit, tangerine juice
Flavan-3-ols	Catechin, epicatechin, galloylated derivatives	Tea, apple, plums, cranberries, berries, chocolate
Flavones	Luteolin, apigenin	Fruits: olives, celery
		Vegetables: hot peppers, fresh parsley, celery hearts
		Spices and herbs: oregano, dry parsley, rosemary, thyme
Anthocyanins	Cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin (mostly as glycosides)	Fruits: Cherries, blackberries, black currants, blueberries, elderberries, black grape, strawberries, plums, cranberry, raspberry, pomegranate juice



Flavone	R_1
Apigenin	H
Luteolin	OH

Fig. 5.1 Chemical structure of flavones and their dietary sources



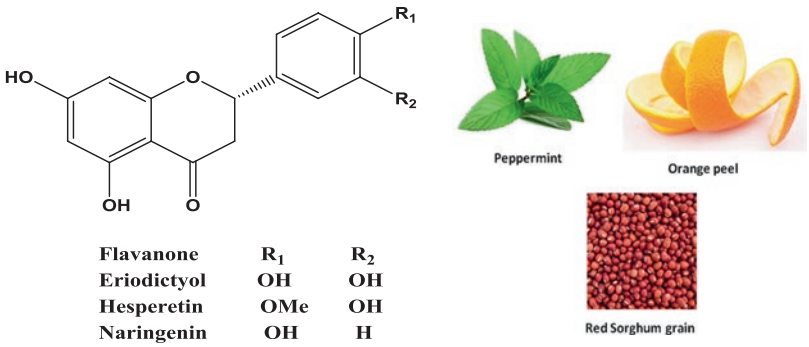
Flavanol	R_1	R_2
Isorhamnetin	OMe	H
Kaempferol	H	H
Myricetin	OH	OH
Quercetin	OH	H

Fig. 5.2 Chemical structure of flavonols and their dietary sources

phenolic rings that link the structural elements: (1) The phenolic acids, which have subclasses derived from different hydroxybenzoic acids, such as gallic acid and hydroxycinnamic acids, containing ferulic, caffeic, and coumaric acids; (2) the giant flavonoid subclass, which consists of the flavones (Fig. 5.1), flavonols (Fig. 5.2), flavanones (Fig. 5.3), flavanols (Fig. 5.4), and anthocyanidins (Fig. 5.5); (3) the stilbenes; and (4) the lignans and their polymers (Lin et al. 2016).

The richest flavonoids in the diet are flavanols (catechins plus proanthocyanidins), anthocyanins, and their oxidation analogues. The leading dietary sources of polyphenols include some common fruits and beverages (tea, coffee, fruit juice, wine, beer, and chocolate) and, to a lesser extent, dries legumes, vegetables, and cereals as shown in Table 5.1 (Bhagwat et al. 2013).

Terpenoids (Figs. 5.6 and 5.7) and Saponins (Fig. 5.8) occur in a wide range of plants but only a few of them are frequently used as food by humans. The more regularly consumed ones are spinach, soybeans, chickpeas, and peanuts. Many different saponins can exist within a sole plant species. Common dietary sources of saponins are soybeans (5.6%), lentil (4%), broad bean (3.7%), chickpeas (3.6%), garden peas (2.5%), and lucerne/alfalfa (2–3%) (Guclu-Ustundag and Mazza 2007).



Flavanone	R_1	R_2
Eriodictyol	OH	OH
Hesperetin	OMe	OH
Naringenin	OH	H

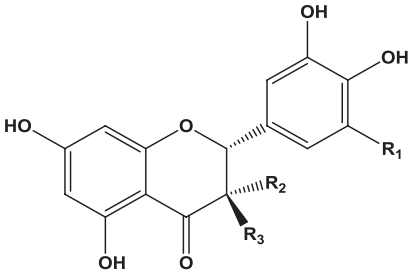
Fig. 5.3 Chemical structure of flavanones and their dietary sources

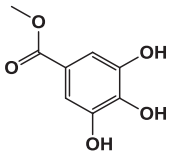
5.3 Dietary Phytochemicals and Cancer

5.3.1 Epidemiological Evidence

Epidemiological studies and systematic analyses have shown the response of diet on health, and the relation between the utilization of certain foods and a marked down risk of some chronic diseases like cancer. In this view, many exercises have proven the potential of dietary phytochemicals as anticarcinogenic agents during study using different cell lines, animal models, and human epidemiological data (Scott et al. 2009; Kapinova et al. 2018). Dietary phytochemicals may inhibit numerous stages in the carcinogenesis mechanism and hence prevent or hold up tumor development. Although induction of apoptosis looks to be rather specific for the cancer cells, it may perhaps be mentioned that certain human studies have exposed no useful effects (Table 5.2). The Korean Population Cohort Study showed that a higher intake of flavonols and flavan-3-ols can slow down the risk of colorectal cancer (Cho et al. 2017). In a Netherlands Cohort Study involving 20,852 people, decreased colorectal cancer risk in normal wt. women was observed on consumption of a flavonol and catechin rich diet (Simons et al. 2009). Similarly, a decreased risk for esophageal, gastric, and prostate cancers have been reported after the consumption of anthocyanidin (Petrick et al. 2015). Also several epidemiological studies showed the pull down of different types of cancer risk after consumption of quercetin, myricetin, catechins, green tea, soy and many more dietry phytochemicals.

In summary, epidemiological and nutritional intervention studies data suggest that high consumption of dietary foods rich in polyphenols, flavonoids, terpenoids, and saponins may shorten the flourishing risk of several types of cancers (breast, colon, rectal, gastric, pancreatic, lung, ovarian, and prostatic cancer). This promising finding has motivated scientists to explore the molecular mechanisms involved in the antitumor actions in order to validate the value for cancer treatment. Various in vitro and in vivo investigations have provided broad evidence to prevent carcinogenesis and to suppress tumorigenesis over different molecular mechanisms.





Gallate

Flavan-3-ol	R_1	R_2	R_3
(+)-Catechin (C)	H	H	OH
(+)-Catechin-3-gallate (CG)	H	H	Gallate
(-)-Epicatechin (EC)	H	OH	H
(-)-Epicatechin-3-gallate (ECG)	H	Gallate	H
(-)-Epigallocatechin (EGC)	OH	OH	H
(-)-Epigallocatechin-3-gallate (EGCG)	OH	Gallate	H
(+)-Gallocatechin (GC)	OH	H	OH
(+)-Gallocatechin-3-gallate (GCG)	OH	H	Gallate

Barley

Cocoa beans

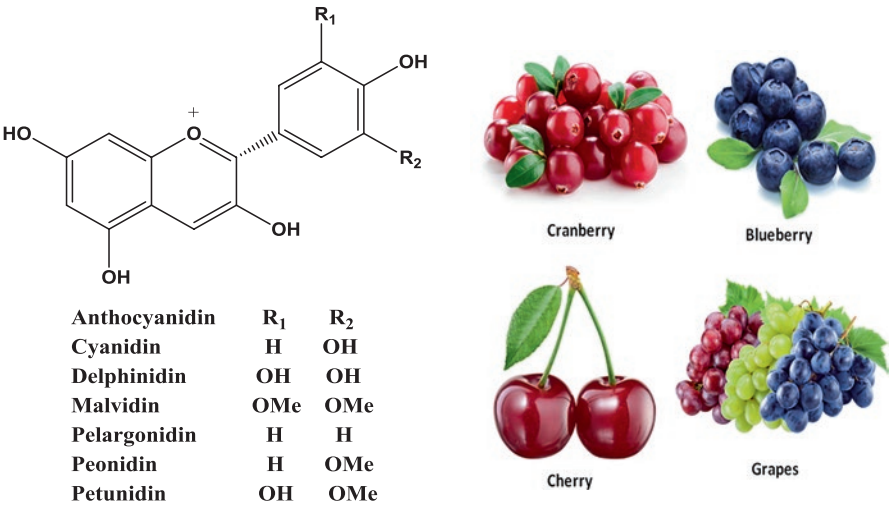
Green tea

Acacia Catechu

Fig. 5.4 Chemical structure of flavan-3-ols and their dietary sources

5.3.2 Dietary Phytochemicals Effects in Xenograft Models

The in vivo effect of dietary phytochemicals has been studied using subcutaneous xenografts in mice. A nude mouse model of breast cancer xenogratfs can reduce the primary tumor growth using combined treatment with resveratrol, quercetin, and catechin (Schlachterman et al. 2008). Anthocyanidins (cyanidin, malvidin, petunidin, peonidin, and delphinidin) at 1.5 mg/mouse inevitably inhibit the development



Anthocyanidin	R_1	R_2
Cyanidin	H	OH
Delphinidin	OH	OH
Malvidin	OMe	OMe
Pelargonidin	H	H
Peonidin	H	OMe
Petunidin	OH	OMe

Fig. 5.5 Chemical structure of anthocyanidins and their dietary sources

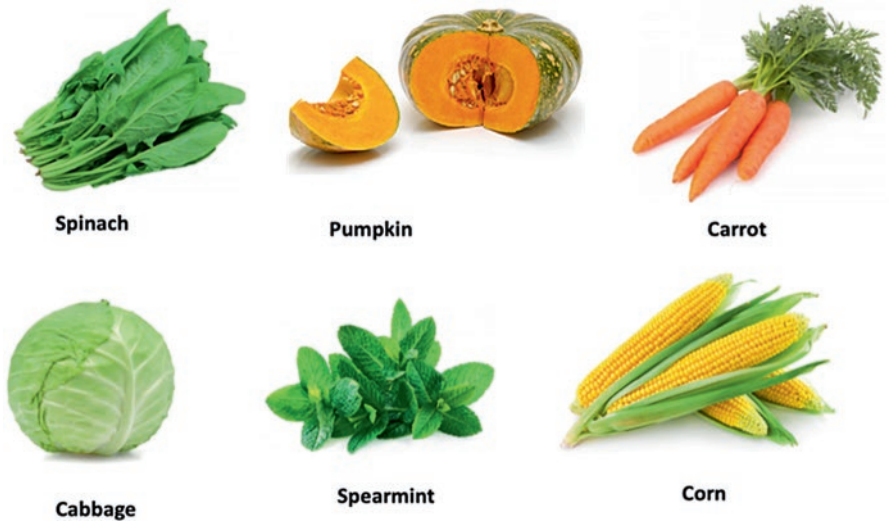


Fig. 5.6 Common dietary sources of terpenoids

of H1299 xenografts in nude mice. Cyanidin, the most active anthocyanidin, reduced the growth by ≈60% and inhibited the growth of xenografts in nude mice (Liu et al. 2018). Significant reduction of tumor growth in a T24 bladder cancer xenograft model has been observed after treatment with the flavonol myricetin (Sun et al. 2012). Similarly, hepatocellar carcinoma xenograft growth is inhibited by flavone apigenin in nude mice (Gao et al. 2018).

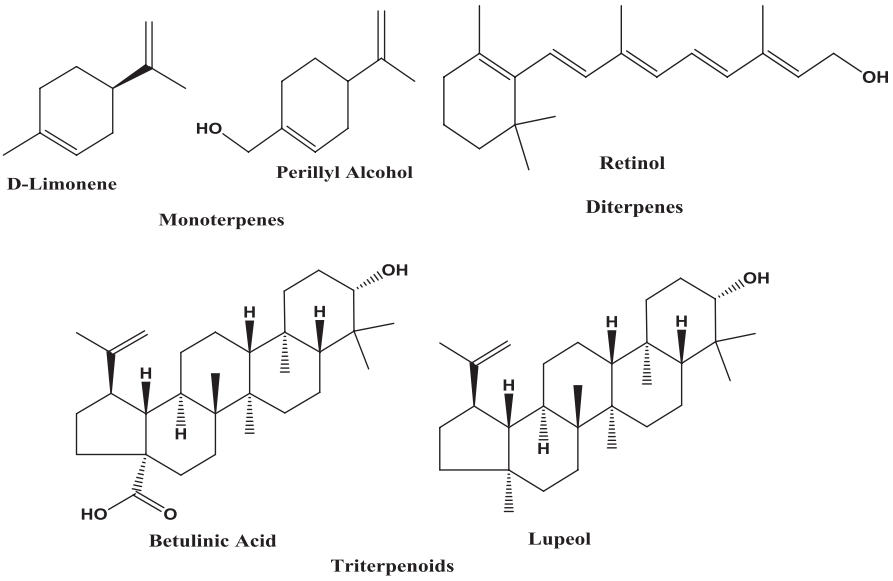


Fig. 5.7 Structure of some common dietary terpenoids

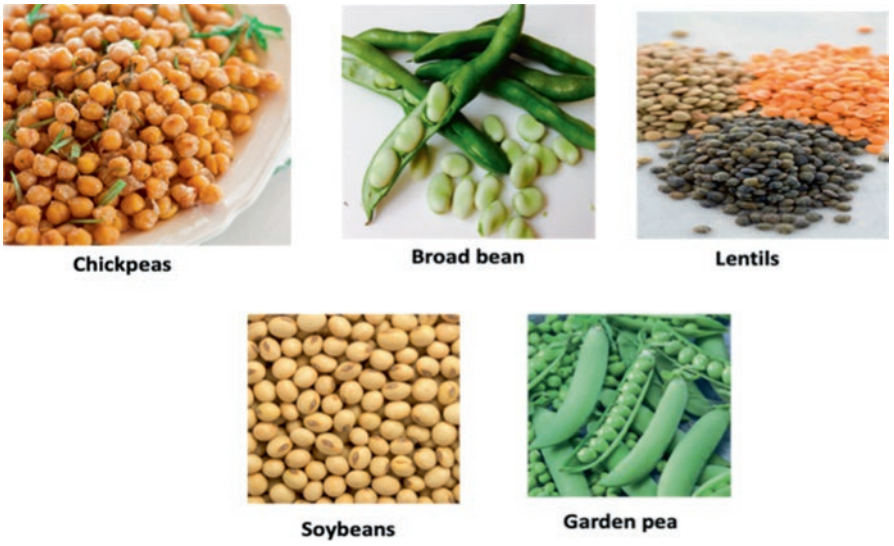


Fig. 5.8 Common dietary sources of saponins

Dietary saponins, such as hederagenin, and the triterpene oleanolic acid also inhibit the tumor growth in a mouse xenograft model (Kim et al. 2017; Niu et al. 2018). Similarly, dietary diterpene carnosol (Johnson et al. 2010), monoterpene geraniol (Kim et al. 2012), and triteppene betulinic acid suppress cancer cell growth in xenograft tumor models (Cai et al. 2018).

Table 5.2 Epidemiological studies: corporation between flavonoids or foods affluent in phenolic compounds and cancer

	Effect	Sample size	References
Flavonoids	Dropped off cancer risk in entire sites combined	9959 men	Knekt et al. (1997)
	Deteriorated cancer risk in the oral cavity, larynx, pharynx and esophagus	540 people	De Stefani et al. (1999)
Quercetin, onions, white grapes	Decreased recurrence of lung cancer	582 people	Le Marchand et al. (2000)
Quercetin	Decreased incidence of lung cancer	10,054 men	Knekt et al. (2002)
	Decreased incidence of colon cancer	264 people	Kyle et al. (2010)
Quercetin, kaempferol	Decreased risk of gastric cancer	354 people	Garcia-Closas et al. (1999)
Catechins	Decreased incidence of epithelial cancer	939 men	Arts et al. (2001)
Tea	Decreased risk of colon cancer	12,170 people	Su and Arab (2002)
Green tea	Slow down risk of prostate cancer	49,920 men	Kurahashi et al. (2008)
	Diminished risk of recurrence breast cancer and metastasis	472 women	Inoue et al. (2001)
Flavonoid intake and black tea	Declined risk of prostate cancer	58,279 men	Geybels et al. (2013)
Soy	Decreased risk of lung cancer	999 men	Wakai et al. (1999)
	Decreased risk of breast cancer	34,759 women	Key et al. (1999)
Anthocyanidin	Reduced risk of oesophageal and gastric cancer	615 people	Petrick et al. (2015)
Flavonol and catechin	Decreased colorectal cancer risk in normal wt. women	120, 852 women	Simons et al. (2009)
	Reduced risk of prostate cancer	118 people	Geybels et al. (2013)
Epicatechin, catechin, quercetin, and kaempferol	Decreased lung cancer risk among tobacco smokers	558 people	Cui et al. (2008)

5.3.3 Dietary Phytochemicals Effects on Apoptosis

Programmed cell death is defined by morphological and biochemical modifications in cells (e.g., DNA fragmentation) (Debatin 2004). Dietary phytochemicals induce apoptosis in various cancer cell lines, namely human breast cancer (Valcic et al. 1996), lung cancer (Yang et al. 1998), gastric cancer (Horie et al. 2005), colon cancer (Tan et al. 2000), and prostate cancer (Brusselmans et al. 2003). Recent investigations have shown that the dietary flavonol quercetin induces apoptotic cell death in various types of cancers, such as leukemia (Chen and Jiu-Hong 2005; Mertens-Talcott and Percival 2005), prostate cancer (Huynh et al. 2003), breast cancer

(Hakimuddin et al. 2004), lung cancer (Nguyen 2003) and hepatoma (Chi et al. 1997). Moreover, these flavonols have also been shown to promote morphological mutation and DNA cleavage in leukemia (Csokay et al. 2005) and rat pancreatic carcinoma cells (BSp73AS) (Mouria et al. 2002).

Genistein has been found to restrain the growth of various cancer cells by the modulation of genes that are related to the control of apoptosis or to another mechanism like cell growth or signal transduction pathways, after all this isoflavonoid is a magnificent inhibitor of protein tyrosine kinases (Lian et al. 1999). It can promote apoptosis in prostate cancer (Kumi-Diaka et al. 2000), breast cancer (Li et al. 1999), head and neck squamous cell carcinoma (Alhasan et al. 1999), lung cancer cells (Lian et al. 1999), and stomach cancer cells (Yanagihara et al. 1993).

Kaempferol exerts a direct effect on the apoptosis extrinsic pathway, which is based on the presence of death receptors on the cell surface able to recognize death inducing substances. These death receptors comprise tumor necrosis factor alpha (TNF-α), FAS, and TRAIL (Lee et al. 2014).

Anthocyanidins have been found to activate morphological change and DNA fragmentation in hepatoma cells (Shih et al. 2005). Cell apoptosis was detected by DNA agarose gel electrophoresis when lung cancer cells NCI-H460 were treated with anthocyanidin (Zhang et al. 2005). Theaflavin digallate and epigallocatechin inhibited growth and promoted apoptosis in COLO 320DM cells (Hsu et al. 2012). Morphological observation of the tissue displayed apoptotic bodies in treated human stomach cancer KATO III cells (Hibasami et al. 1998). Viability, apoptosis, and DNA fragmentation assay indicated that the merger of EGCG and bleomycin potentiated apoptosis (Bimonte et al. 2015). Epigallocatechin-3-O-gallate provoked dose-dependent cell propagation inhibition, cell cycle detention at the G0/G1 stage, and DNA cleavage in HT-1080 cells, suggesting the induction of apoptosis (Lee et al. 2011). Synergistic apoptosis of HCT 15, HCT 116, as well as Hep G-2 cells by curcumin and catechin have been observed efficiently (Alam et al. 2018). Anthocynin rich bilberry extract has been shown to induce apoptosis in HL60 cells and nucleosomal DNA fragmentation (Katsube et al. 2003). Triterpenes oleanolic acid and ursolic acid induced apoptosis in four cancer cell lines of human liver. Completion of apoptosis was proved microscopically by observing escalation in plasma membrane permeability and detecting the fragmentation of DNA (Shyu et al. 2010).

5.3.4 Epigenetic Markers Effects

Dietary factors play a pivotal role in many natural biological courses of action and are also convoluted in the surveillance of pathological breakthroughs. Environmental and dietary circumstances can influence diseases linked to genetic and epigenetic modifications. Recently, an increasing number of nutritional components that have an inherent epigenetic activity have been identified. These micronutrients are able to control gene expression by carrying out an inheritable DNA (or DNA-associated proteins) modification without altering the DNA sequence. The posttranslational modification of histone proteins is the most well-known epigenetic mechanism by histone

deacetylases (HDACs). Synthetic HDACs cause harmful side effects like atrial fibrillation, questioning their applicability. Therefore, the discovery of new HDACs inhibitors (HDACIs) is of great interest as potential anticancer drugs (Berger et al. 2013).

Dietary polyphenols and flavonoids have a custodial role against diseases and have found an important place in cancer prevention (Yang et al. 1998; Tan et al. 2000). In fact, various mechanisms have been found that aid in demonstration of the preventive nature of polyphenols, along with their ability to amend the epigenome by chromatin remodeling or by reactivating silenced genes in cancer cells (Bag and Bag 2018). Their chemopreventive potential can be defined by their ability to restrain DNMTs and also act as histone modifiers. The epigenome of cancer cells could be changed significantly by both of these properties, and they are viewed as interesting possibilities for anticancer therapeutics (Fig. 5.9).

The DNMT inhibitory activity of a green tea catechin and epigallocatechin 3-gallate (EGCG) was described by Morris et al. (2016). More than 50% of effective compounds in green tea are EGCG. Flavones apigenin and luteolin, flavanone hesperetin, and anthocyanidin cyanidine inhibit DNMT activity when tested in vitro. The flavone apigenin shows chemopreventive properties against prostate cancer by inhibiting HDAC (Ganai 2017). The dietary flavone luteolin influenced apoptosis of HL-60 cells, is associated with c-Jun activation, and expressed the histone H3 acetylation-mediated by Fas/FasL (Wang et al. 2018). It also cut down protein levels and the enzyme actions of epigenetic modifying enzymes, such as DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), in HCT116 cells (Zuo et al. 2018). Delphinidin, a dominant anthocyanidin compound found in diversified fruits, promotes p53-mediated apoptosis by abolishing HDAC activity and stimulating p53 acetylation in human prostate cancer LNCaP cells (Jeong et al. 2016).

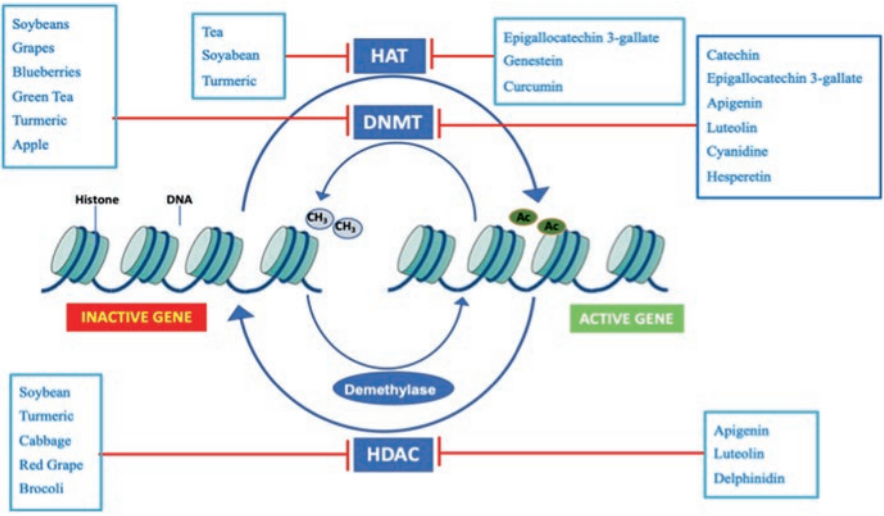


Fig. 5.9 Epigenetic modifications by dietary phytochemicals. (Idea adapted from Szyf 2015)

5.3.5 Importance of Dietary Phytochemicals in Co-therapy

Used in combination, dietary phytochemicals also have great potential to enhance the therapeutic effects of antitumor drugs, a practice known as co-therapy. The combination of the flavonol kaempferol with classical chemotherapeutic agents results in greater cytotoxic effects than those achieved by each of them separately (Luo et al. 2010). It is also able to sensitize the cytotoxic effects of 5-fluorouracil to the tumor cells, cytarabine (Mohan et al. 2013) and doxorubicin (Sharma et al. 2007).

Combination of autophagy inhibitors with the flavone apigenin inhibits the cell proliferation and induces autophagy by way of suppressing the PI3K/Akt/mTOR pathway (Yang et al. 2018).

A synergistic cytotoxic effect by theaflavin-3,3′-digallate, a black tea polyphenol, and cisplatin (CDDP) was shown in cisplatin resistant ovarian cancer cells A2780/CP70 and OVCAR3 (Pan et al. 2018).

Another polyphenol, epigallocatechin-3-gallate, found in tea combined with cisplatin significantly shortened the size of the tumor (Zhou et al. 2014). It also potentiated the effect of adriamycin in CaEs-17 cells (Fantini et al. 2015), fluorouracil in Hep G2 cells (Yang et al. 2012), and ponatinib in chronic myeloid leukemia cells (Goker et al. 2014). Combination of capecitabine with (-)-epigallocatechin-3-gallate inhibits tumor growth and angiogenesis with gastric cancer xenografts in nude mice (Wu et al. 2012). Green tea catechins augmented the antitumor properties of doxorubicin for chemoresistant liver cancer in a mouse model (Liang et al. 2010).

The anthocynidin delphinidin (DPN) in combination with 5-aza-2-deoxycytidine (AzaC) showed the highest inhibition of cell growth in human glioblastoma LN18 and U87MG cells (Chakrabarti and Ray 2015). Anthocyanins also potentiated the activity of trastuzumab in human epidermal growth factor receptor 2-positive breast cancer cells in vitro and in vivo (Liu et al. 2014).

Luteolin with lapatinib inhibited the growth of breast cancer cells (Zhang et al. 2017) and the doxorubicin-induced autophagy in human osteosarcoma U2OS cells (Zhang et al. 2015). The combination of the oncolytic adenovirus CD55-TRAIL with luteolin significantly decreased cytotoxicity in lung/bronchial normal epithelial cells compared with single treatment (Xiao et al. 2017). Co-treatment of tamoxifen and naringenin could inhibit cell proliferation more effectively in ER+ breast cancer cells (Xu et al. 2018). Combination of myricetin with 5-fluorouracil chemotherapy can enhance tumor chemosensitivity of esophageal cancer EC9706 cells, and hence myricetin could be a potential chemosensitizer for esophageal cancer therapy (Wang et al. 2014).

Combination of afromosin with soyasaponin I enhanced their antitumor promoting activity. Consequently, many active compounds were found that might be valuable chemopreventive agents (Konoshima et al. 1992).

Limonene enhances the antitumor effect of docetaxel against prostate cancer cells without being toxic to normal prostate epithelial cells (Rabi and Bishayee 2009). Geraniol in combination with gemcitabine induced BXPC-3 cell apoptosis (Jin et al. 2013). Co-treatment 5-fluorouracil with triterpenoid lupeol induced

apoptosis by upregulating the expressions of Bax and p53 and downregulating the expressions of survivin and Bcl-2 (Liu et al. 2016).

5.4 Concluding Remarks

In the past few decades, several studies have been performed that support the concept of cancer chemoprevention dietary polyphenols, flavonoids, terpenoids, and saponins. Several epidemiological studies have corroborated that dietary consumptions have a huge impact on cancer prevalence. Owing to these encouraging observations, research efforts all across the globe have focused on identifying, characterizing, and providing the scientific basis behind the chemopreventive properties of dietary supplements. The results have shown that fruits and vegetables represent an untapped reservoir of various nutritive and nonnutritive phytochemicals that when incorporated into a healthy lifestyle can be a very useful step toward cancer chemopreventive.

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