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REVIEW

Epigenetic targets of bioactive dietary components for cancer prevention and therapy

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Abstract The emergent interest in cancer epigenetics stems from the fact that epigenetic modifications are implicated in virtually every step of tumorigenesis. More interestingly, epigenetic changes are reversible heritable changes that are not due to the alteration in DNA sequence but have potential to alter gene expression. Dietary agents consist of many bioactive ingredients which actively regulate various molecular targets involved in tumorigenesis. We present evidence that numerous bioactive dietary components can interfere with various epigenetic targets in cancer prevention and therapy. These agents include curcumin (turmeric), genistein (soybean), tea polyphenols (green tea), resveratrol (grapes), and sulforaphane (cruciferous vegetables). These bioactive components alter the DNA methylation and histone modifications required for gene activation or silencing in cancer prevention and therapy. Bioactive components mediate epigenetic modifications associated with the induction of tumor suppressor genes such as

p21^{WAF1/CIP1} and inhibition of tumor promoting genes such as the human telomerase reverse transcriptase during tumorigenesis processes. Here, we present considerable evidence that bioactive components and their epigenetic targets are associated with cancer prevention and therapy which should facilitate novel drug discovery and development. In addition, remarkable advances in our understanding of basic epigenetic mechanisms as well as the rapid progress that is being made in developing powerful new technologies, such as those for sensitive and quantitative detection of epigenetic and epigenomic changes in cancer biology, hold great promise for novel epigenetic approaches to cancer prevention and therapy.

Keywords Bioactive component · Dietary polyphenol · Cancer · Epigenetic · DNA methylation · Histone modifications

Introduction

Natural dietary agents including fruits, vegetables, and spices have been showing great potential in preventing and treating a wide variety of diseases including cancers. Dietary agents consist of many bioactive compounds that are ubiquitous in plants, many of which have been used as ancient traditional medicines. Dietary agents are not only an excellent source of fiber, vitamins, and minerals, but also contain bioactive components such as polyphenols, alkaloids, and phenolics that may serve more than a basic nutrition function. The bioactive components of dietary phytochemicals most often shown to be effective against cancer are tea polyphenols, genistein, curcumin, resveratrol, sulforaphane, isothiocyanates, silymarin, diallyl sulfide, lycopene, rosmarinic acid, apigenin, and gingerol. These

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bioactive components have shown great potential in preventing cancer through modifying genetic and epigenetic targets. In this analysis, we will focus on epigenetic targets of these bioactive dietary supplements associated with cancer prevention and therapy.

Epigenetics and cancer

“Geneticists study the gene; however, for epigeneticists, there is no obvious ‘epigene’” (Bird 2007). Nevertheless, epigenetics is typically defined as the study of reversible heritable changes in gene expression that are not due to alterations in DNA sequence. The term ‘epigenetic’ was coined by the developmental biologist, Conrad Hal Waddington, in 1942. Robin Holliday defined epigenetics as the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms (Holliday 1990). One of the best examples of epigenetic changes in eukaryotic biology is the different developmental stages from the single fertilized egg, the zygote, to a fully grown organism. Modern biology uses epigenetic changes as molecular tools for finding and treating various diseases including cancer. Cancer is a multi-step process derived from combinational crosstalk between genetic alterations and epigenetic influences through various environmental factors (Ducasse and Brown 2006; Esteller 2008; Ellis et al. 2009). Moreover, it has been well documented that environmental exposure to nutritional, dietary, physical, and chemical factors could alter gene expression and modify individual genetic susceptibility through changes in the epigenome (Issa 2008; Suter and Aagaard-Tillery 2009; Herceg 2007). Several distinct but intertwined mechanisms are known to be part of the epigenome which includes DNA methylation, histone acetylation, poly-ADP-ribosylation and ATP-dependent chromatin remodeling.

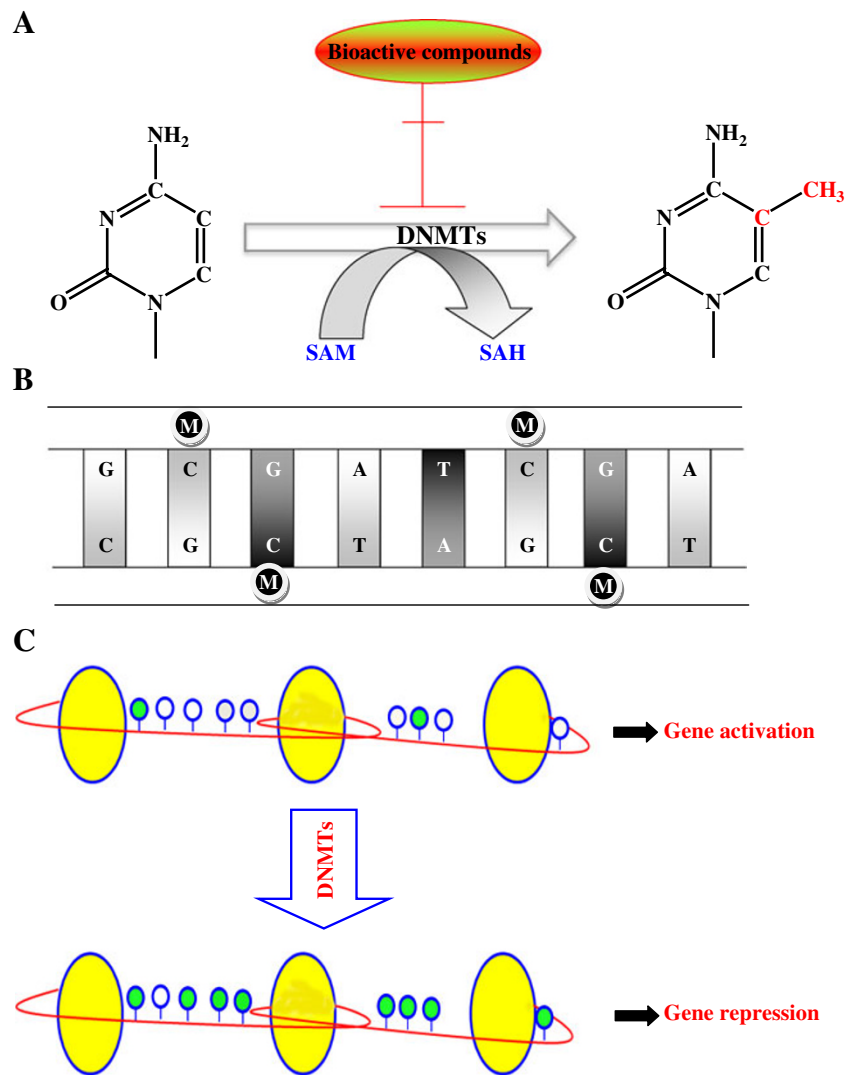
Epigenetic mechanisms controlling gene transcription are often involved in cell proliferation, differentiation, and survival and are casually linked with malignant development. Alterations in epigenetic processes including chromatin modifications such as DNA methylation and histone acetylation are common targets studied in cancer epigenomics (Herceg 2007; Esteller 2007). It has been shown that half of all tumor suppressor genes are inactivated in cancers more often by epigenetic, than by genetic, mechanisms (Issa 2008). Growing evidence suggests that bioactive dietary components impact epigenetic processes often involved with reactivation of tumor suppressor genes, activation of cell survival proteins, and induction of cellular apoptosis in many types of cancer (Landis-Piwowar et al. 2008; Li et al. 2010; Paluszczak et al. 2010; Majid et al. 2008). In addition to transcriptional silencing of tumor suppressor genes and

protein expression, noncoding microRNAs (miRNAs) can regulate expression of a myriad of cellular proteins by affecting mRNA stability and translation by epigenetic processes in cancer progression (Esteller 2007; Ducasse and Brown 2006). Interestingly, these miRNAs can control the expression of various epigenetic modifying enzymes such as DNA methyltransferases (DNMTs), histone methyltransferases (HMTs), and histone deacetylases (HDACs) involved in carcinogenesis processes (Guil and Esteller 2009; Saito and Jones 2006). Recent evidence suggests that bioactive dietary components can also target various oncogenic or tumor suppressive miRNAs to alter the gene expression profile in cancer prevention (Parker et al. 2009; Sun et al. 2009; Li et al. 2009b). In fact, miRNA profiles are now being used to classify human cancers (Calin et al. 2004). Further, miRNAs can directly or indirectly regulate cancer progression either by acting as tumor suppressors or by altering epigenetic modifying enzymes, respectively. In particular, miRNA-221 and miRNA-222 target *KIT*, an oncogene, and therefore function as tumor suppressors in erythroblastic cells and other human solid tumors (Croce 2009). Furthermore, the miRNA-29 family can directly regulate the expression of DNMTs and increase expression of DNMT3a and DNMT3b thereby causing a global genomic hypermethylation and silencing of methylation-sensitive tumor suppressor genes such as *FHIT* and *WWOX* (Fabbri et al. 2007).

DNA methylation

DNA methylation involves the covalent addition of a methyl group to cytosines in eukaryotic DNA. DNA methylation typically occurs at CpG dinucleotides, whereas non-CpG methylation is often found in embryonic stem cells. Moreover, 60–90% of all dispersed CpG sequences are methylated in mammals, whereas, unmethylated CpGs are grouped in clusters called “CpG islands” that are present in the 5'-regulatory regions of many genes. The DNA methylation state is maintained primarily by DNMTs, which catalyze the transfer of a methyl group from the methyl precursor, *S*-adenosyl-L-methionine (SAM), onto the 5-position of certain cytosines in CpG dinucleotides (Fig. 1). Multiple DNMTs are known to be present in humans, animals, and microorganisms, and they have varying degrees of specificity toward unmethylated and hemimethylated DNA substrates (Bestor 2000). SAM is the methyl donor in DNMT-mediated DNA methylation, as in many other enzymatic methylation reactions [such as the catechol-*O*-methyltransferase (COMT)-mediated *O*-methylation of various catechol substrates], resulting in the formation of *S*-adenosyl-L-homocysteine (SAH) after donating its methyl group to the DNA substrate.

Fig. 1 Schematic diagram illustrating DNA methylation catalyzed by DNMTs. **a** The DNA methylation process is catalyzed by the DNMTs by adding a methyl group (CH₃) from SAM to the 5-position of the cytosine ring. SAM donates a methyl group and is then converted into SAH. **b** Methylated cytosine moieties in CpG dinucleotides within a gene promoter. **c** DNMTs convert unmethylated DNA into methylated DNA in chromatin. *White circles* unmethylated CpG sites, *green circles* hypermethylated CpG sites, *yellow circles* histone proteins, *red thread* DNA



In many disease processes such as cancer, gene promoter CpG islands acquire abnormal hypermethylation by altering DNMT expression and activity, which results in heritable transcriptional gene silencing. DNA methylation may impact the transcription of genes in two major ways. First, the methylation of DNA prevents binding of sequence specific transcriptional factors (e.g., AP-2, E2F, c-Myc) that require the presence of unmethylated CpG within the binding sites (Tate and Bird 1993). Second and likely more important is that methylated DNA may be bound by proteins known as methyl-CpG-binding domain (MBD) proteins. MBD proteins then recruit additional proteins, such as histone deacetylases and other chromatin-remodeling proteins that can modify acetylation and methylation status of histones to the locus thereby inhibiting transcriptional access to the chromatin. This subsequently leads to the formation of compact, inactive chromatin (Wade 2001; Ballestar and Wolffe 2001). The clinical aspects of DNA methylation are very important

especially since DNA methylation is a reversible process and thereby leads to silencing or activation of particular genes for disease progression including cancer (Laird 2005).

In higher eukaryotes, DNA methylation is an enzymatic process that is primarily mediated by three enzymes; DNMT1, DNMT3a, and DNMT3b (Bestor 2000). DNMT1 is a ubiquitous enzyme considered the major methyltransferase for maintenance methylation, and the other two DNMTs serve as *de novo* methyltransferases. In human cells, DNMTs have some overlap in *de novo* and maintenance function. DNMTs have been showed to be an extensive molecular drug target for many available FDA-approved epigenetic drugs such as 5-azacytidine, commercially available as Vidaza, and 5-aza-2'-deoxycytidine, commercially available as Dacogen (Grønbaek et al. 2007; Kaminskas et al. 2005). In addition, the DNMT1 antisense oligonucleotide referred to as MG98 is currently under phase I clinical trials for patients with advanced solid tumors (Plummer et al. 2009). However, many of the most commonly used drugs

produce meaningful results in less than half of the patients, and the use of higher doses often results in adverse side effects (Grønbaek et al. 2007). Another derivative of 5-azacytidine, zebularine, appears to be more stable than 5-azacytidine or 5-aza-2'-deoxycytidine, but has very narrow specificity towards cancer cells (Hellebrekers et al. 2007). Therefore, many cancer patients are exposed to highly toxic drugs and suffer from adverse side effects while receiving few therapeutic benefits (Eisenberg et al. 1998). Hence non-toxic and more effective dietary bioactive components have received wide attention in the use against various cancers for prevention and therapy. Extensive results have shown that bioactive dietary components have great potential in altering DNA methylation by modifying DNMTs levels in cancer prevention and therapy (Li and Tollefsbol 2010).

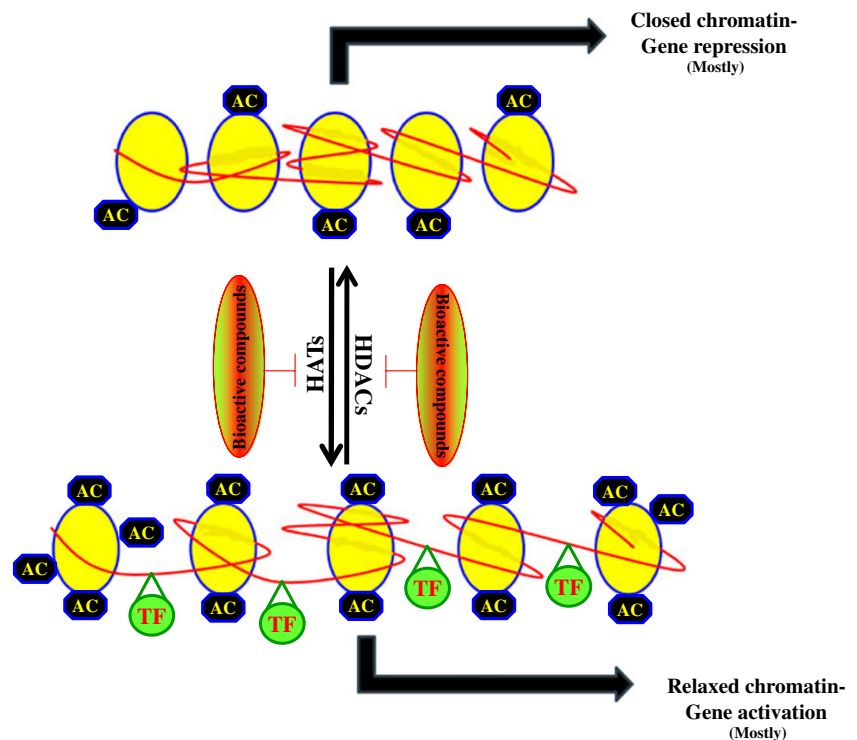
Epigenetic regulation has attracted considerable interest as a molecular target for cancer prevention and therapy as well as a target of bioactive food components. Many bioactive dietary components have shown promising results in direct or indirect inhibition of DNMT activity in cancer prevention and therapy. For example, (–)-epigallocatechin-3-gallate (EGCG), a major component of green tea, is known to complex with the DNMTs which reduces methylating activity in cancer cells leading to cancer prevention or therapy through epigenetic mechanisms (Fang et al. 2003; Mittal et al. 2003; Tsao et al. 2009). Furthermore, daily oral intake of EGCG in the form of Polyphenon E, a green tea extract, was well tolerated by

chronic lymphocytic leukemia patients in phase I clinical trials (Shanafelt et al. 2009).

Histone modifications

Many histone modifications play important roles in epigenetic alterations, and acetylation and methylation are the two main histone modifications that have been clinically linked as predictors for cancer progression (Davis and Ross 2007; Fraga et al. 2005; Seligson et al. 2005). These histone modifications induce chromatin alterations that allow access to the various transcriptional activators and/or repressors at gene promoters, and they therefore play an important role in gene regulation and tumorigenesis (Fig. 2) (Ganesan et al. 2009; Dalvai and Bystricky 2010; Sharma et al. 2010). Histones are subject to different types of reversible covalent posttranslational modifications including, but not limited to, lysine acetylation, lysine and arginine methylation, serine and threonine phosphorylation, and lysine ubiquitination and sumoylation. These modifications occur primarily within the histone amino-terminal tails protruding from the surface of the nucleosome as well as on the globular core region and regulate key cellular processes such as transcription, replication, and repair (Kouzarides 2007). Specific histone modifications appear to act as programmed “codes” which can be identified by specific proteins to bring about distinct downstream events such as

Fig. 2 Schematic representation of histone modifications. HATs induce relaxed chromatin which allows access to the various transcriptional factors associated with gene activation. HDACs induce closed chromatin associated with gene repression. Various bioactive compounds such as EGCG, sulforaphane, and curcumin are linked with alterations of both HATs and HDACs. *Yellow circle* histone protein, *red thread* DNA; *AC* acetylation, *TF* transcription factor



transcriptional activation or repression. The mechanism of inheritance of this histone code, however, is still not fully understood.

DNA methylation often suppresses gene expression, with some exceptions like the human telomerase reverse transcriptase (*hTERT*) gene (Berletch et al. 2008; Li et al. 2009a). Nevertheless, gene repression or activation is not determined by histone acetylation or methylation in general, but rather is determined by which residue is being modified, for example, trimethylation of lysine 4 on histone H3 (H3K4me3) is enriched for transcriptional gene activation, whereas trimethylation of lysine 9 on histone H3 (H3K9me3) and trimethylation of lysine 27 on histone H3 (H3K27me3) is present at gene promoters for transcriptional repression (Hebbes et al. 1988; Choudhuri et al. 2010). Further, enrichment of acetylation at lysine residues at gene promoter regions is associated with gene activation (Hebbes et al. 1988). Histone acetylation enhances chromatin accessibility by neutralizing the DNA–histone interactions which results in a relaxed, open chromatin conformation that allows the transcriptional activators to gain access to their cognate recognition elements and initiate/enhance transcription (Fig. 2) (Görisch et al. 2005; Lafon-Hughes et al. 2008).

Histone modifications are catalyzed by many enzymes such as histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases (HMTs), and histone demethylases (HDMs). HATs and HDACs add and remove acetyl group to the lysine residues present in histones, respectively, whereas HMTs and HDMs add and remove methyl groups to the different lysine or arginine residues in histones, respectively (Choudhuri et al. 2010). Further, arginine methylation is presumably transcription activating, whereas lysine methylation can cause either transcriptional activation or repression, depending on which lysine residue is being methylated (Choudhuri et al. 2010). Histone hypoacetylation at a promoter region, induced by either lack of HAT function or increased HDAC activity, results in silencing of the tumor suppressor gene, *p21^{WAF1/CIP1}*, in tumorigenesis (Majid et al. 2008; Kikuno et al. 2008). By contrast, histone hyperacetylation at certain promoters through either increased HAT activity or decreased HDAC activity, results in an activation of normally repressed genes (Acharya et al. 2005; Kim et al. 2003). Collectively, the aberrant enrichment of HAT and HDAC activities may trigger carcinogenesis processes (Mottet and Castronovo et al. 2008).

It has been widely recognized that HDACs are promising targets in the field of oncology and epigenetic therapy (Davis and Ross 2007; Marsoni et al. 2008). An impressive body of preclinical research points to the ability of HDAC inhibitors (HDACIs) to modulate a wide variety of cellular functions, including cellular differentiation, cell cycle progression, apoptosis, cytoskeleton modifications, and

angiogenesis (Marsoni et al. 2008). Thus, the use of HDACIs is considered a potent strategy in cancer prevention and epigenetic therapy. An extensive list of HDACIs has been purified from natural sources or synthetically developed, and many of these HDACIs have advanced to clinical applications (Bolden et al. 2006). HDACIs such as trapoxin, trichostatin A, and suberoylanilide hydroxamic acids (SAHAs) are among the most studied and have more global HDAC inhibition activity. Vorinostat or SAHA (brand name Zolinza) is a commercially available FDA-approved HDACI for treatment of cutaneous T-cell lymphoma (Ellis et al. 2009). Many other HDACIs are in different phases of clinical trials such as panobinostat (LBH589), belinostat (PXD101), TF2357, PCI-24781, phenylbutyrate, romidepsin (depsipeptide), MS-275, MS-275 and, MGCD0103 (Ellis et al. 2009).

Besides synthetic HDACIs, many bioactive dietary components have shown promising results in direct or indirect inhibition of HDAC activity as well as other histone modification activities in cancer prevention and therapy (Nian et al. 2009; Myzak et al. 2006c). For example, sulforaphane (SFN), a major component present in cruciferous vegetables, inhibits HDAC activity, at least partially, by direct interaction with the HDAC active sites (Myzak et al. 2004). In another study, SFN has been shown to result in HDAC inhibition in human volunteers consuming SFN-rich broccoli sprouts, and the SFN-induced HDAC inhibition increased histone acetylation in peripheral blood cells of the human subjects without adverse effects (Myzak et al. 2006a, 2007).

Bioactive dietary components and epigenetic targets

For more than a decade, there has been considerable interest in the use of naturally occurring botanicals for the prevention of diseases, including cancers. Beverages, fruits, vegetables, and other components of the human diet commonly contain polyphenols which have been shown in many investigations to have chemopreventive and anti-cancer properties (Aggarwal and Shishodia 2006; Meeran and Katiyar 2008; Yang et al. 2001). Different nutrients, specifically dietary botanicals, can play a role in the regulation of both normal and pathologic processes. An improved understanding of the regulatory role of these nutrients on various molecular targets may help in the prevention and treatment of various cancers. Although several dietary agents or nutrients regulate different molecular targets in various cancers, here we summarize the role of some common bioactive dietary agents and their epigenetic targets on various cancers. The agents which we discuss include tea polyphenol–catechins (green tea), curcumin (turmeric), genistein (soybean), resveratrol

(grapes), SFN (cruciferous vegetables), and other bioactive components such as apigenin (parsley), baicalein (Indian trumpet), cyanidins (grapes), isothiocyanate (cruciferous vegetables), rosmarinic acid (rosemary), and silymarin (milk thistle). A brief discussion includes their epigenetic targets in cancer cells both in vitro and in vivo leading to their multiple roles in the regulation of cancer prevention and therapy. Some of the most commonly used bioactive dietary components, including their source, botanical name, and their epigenetic targets associated with tumorigenesis are summarized in Table 1.

Tea polyphenols

DNA methylation

The tea plant *Camellia sinensis* is cultivated in more than 30 countries. Tea is consumed worldwide and next to water is the most consumed beverage in the world, with an average per capita consumption of ~120 mL/day (Mukhtar and Ahmad 2000). Epidemiologic observations and laboratory studies have indicated that polyphenolic compounds present in tea may reduce the risk of a variety of diseases, including coronary heart disease and cancer. The most abundant chemical compound in green tea beverages is catechins, which include (–)-epicatechin (EC), (–)-epicatechin-3-gallate (ECG), (–)-epigallocatechin (EGC), and (–)-epigallocatechin-3-gallate (EGCG) (Graham 1992). Of these, EGCG accounts for more than 50% of the total polyphenol and effective content in green tea (Lin and Liang 2000). EGCG has been identified as a major and most effective constituent of green tea. Therefore, the large majority of the in vitro and in vivo studies of the effects of green tea have been conducted using EGCG.

EGCG has been shown to induce apoptosis and cell cycle arrest in many cancer cells without affecting normal cells (Ahmad et al. 1997; Gu et al. 2009). Therefore, it is likely that EGCG imparts its anti-cancer effects through many different mechanisms (Balasubramanian et al. 2010; Fassina et al. 2004; Huh et al. 2004). One mechanism includes the inhibition of DNMT1 leading to demethylation and reactivation of methylation-silenced genes. Treatment of human esophageal KYSE 510 and 150 cells with EGCG has been shown to lower DNMT1 activity and to lead to hypomethylation and re-expression of genes including *p16^{INK4a}*, retinoic acid receptor β (*RAR* β), *O*⁶-methylguanine methyltransferase (*MGMT*), and human *mutL* homologue 1 (*hMLH1*) (Fang et al. 2003). In another study with oral carcinoma cells, EGCG partially reversed the hypermethylation status of *RECK*, a tumor suppressor gene, and significantly enhanced the expression level of *RECK* mRNA. EGCG-induced epigenetic reactivation of *RECK* is

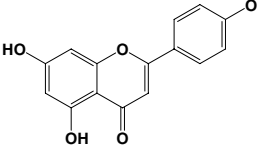

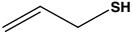

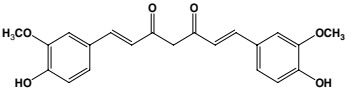

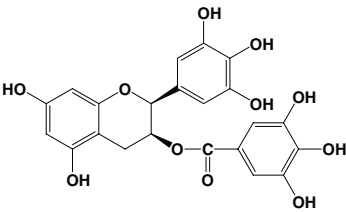

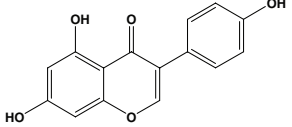

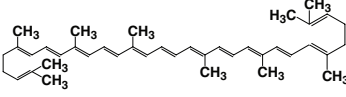

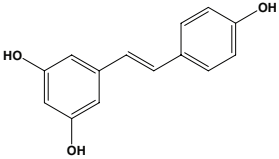

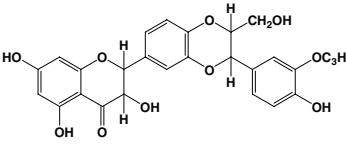

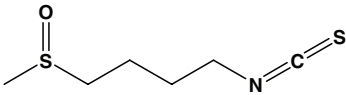

important since it negatively regulates matrix metalloproteinases (MMPs) and inhibits tumor invasion, angiogenesis, and metastasis (Kato et al. 2008). Pandey et al. (2010) demonstrated that exposure of human prostate cancer LNCaP cells to 1–10 μ g/ml of green tea polyphenol for 1–7 days caused a concentration- and time-dependent re-expression of a known precursor to the genesis of prostate cancer, glutathione-S-transferase pi (*GSTP1*), which correlated with DNMT1 inhibition.

Recently, it has been observed that tea polyphenols [catechin, epicatechin, and EGCG and bioflavonoids (quercetin, fisetin, and myricetin)] inhibited SssI DNMT- and DNMT1-mediated DNA methylation in a concentration-dependent manner. The IC₅₀ values for catechin, epicatechin, and various flavonoids ranged from 1.0 to 8.4 μ M, but EGCG was a more potent inhibitor, with IC₅₀ values ranging from 0.21 to 0.47 μ M (Lee et al. 2005). A molecular modeling study demonstrated that EGCG exerts its inhibitory effect on DNMT1 function by blocking entry of the key nucleotide cytosine into its active site by hydrogen bonds and, thus, prevents DNA methylation (Fang et al. 2003). Furthermore, the presence of Mg²⁺ can enhance the binding force of EGCG and the DNMTs by stabilizing their binding interactions nearly ten times more than without Mg²⁺ presence (Lee et al. 2005). Here, we discuss most of the epigenetic targets altered by EGCG, but other catechins such as EC, ECG, and EGC have also been found to share similar properties although they are less efficient than EGCG (Fang et al. 2003; Lee et al. 2005).

Besides direct inhibition of DNMT by EGCG, it was also reported that consumption of polyphenols could lead to a decrease in available *S*-adenosyl-L-methionine (SAM) and an increase in *S*-adenosyl-L-homocysteine (SAH) and homocysteine levels, thereby providing evidence of an indirect inhibition of DNA methylation by EGCG (Lee and Zhu 2006). This conjecture is supported by animal studies demonstrating that EGCG consumption through drinking water can moderately decrease the level of SAM (without increasing the level of SAH) in the intestine (Fang et al. 2007).

EGCG not only reactivates tumor suppressor genes by inhibiting DNA methylation but also inhibits tumor promoter genes such as *hTERT*, a catalytic subunit of telomerase (Berletch et al. 2008). In most cases, hypermethylation of the regulatory region of a gene can inhibit its expression. For example, the *p16^{INK4a}* promoter becomes methylated during tumorigenesis leading to inhibition of its expression (Lee et al. 2003). Interestingly, *hTERT* regulation by DNA methylation goes against the paradigm, and hypermethylation of its promoter leads to increased expression in cancer cells (Guilleret and Benhattar 2004; Quante et al. 2005). One possible reason for this paradox was shown in breast cancer cells were EGCG-

Table 1 Bioactive dietary compounds—their source, molecular structure, and epigenetic targets

Dietary agents	Structure	Epigenetic effect on Cancer*	Picture of the sources
Apigenin (Parsley) ¹ (<i>Petroselinum</i> <i>m</i>) ²		DNMT inhibitor (Fang M et al 2007)	
Allyl Mercaptan (Garlic) ¹ (<i>Allium sativum</i>) ²		HDAC inhibitor (Lea et al 2001; Druesne et al 2004)	
Curcumin (Turmeric) ¹ (<i>Curcuma longa</i>) ²		DNMT inhibitor (Liu et al 2009; Fang et al 2007; Fu and Kurzrock 2010) HDAC and HAT inhibitor (Chen et al 2007; Liu et al 2005; Kang et al 2006; Cui et al 2007; Balasubramanyam et al 2004)	
Epigallocatechin-3-gallate (EGCG) (Green tea) ¹ (<i>Camellia sinensis</i>) ²		DNMT inhibitor (Fang et al 2003; Kato et al 2008; Pandey et al 2010; Lee et al 2005) HAT inhibitor (Choi et al 2009)	
Genistein (Soybean) ¹ (<i>Glycine max</i>) ²		DNMT inhibitor (Majid et al 2008; Kikuno et al 2008; Fang et al 2005; Li et al 2009) HDAC inhibitor and HAT activator (Fang et al 2005; Li et al 2009; King-Batoon et al 2008; Majid et al 2008)	
Lycopene (Tomatoes) ¹ (<i>Solanum lycopersicum</i>) ²		Demethylates the <i>GSTP1</i> , <i>RARβ2</i> and <i>HIN-1</i> genes in breast cancer cells (MDA-MB-231 and MCF10A) (King-Batoon et al 2008)	
Resveratrol (Red grapes) ¹ (<i>Vitis vinifera</i>) ²		DNMT inhibitor (Papoutsis et al 2010; Stefanska et al 2010) SIRT1 activator (Kaerberlein et al 2008; Wang et al 2008; Boily et al 2009)	
Silymarin (Milk thistle) ¹ (<i>Silybum marianum</i> L.) ²		SIRT1 activator (Li et al 2007)	
Sulforaphane (Cruciferous vegetables) ¹ (<i>Brassicaceae</i>) ²		DNMT inhibitor (Meeran et al 2010; Traka et al 2005) HDAC inhibitor (Myzak et al 2007; Dashwood and Ho 2007; Ho et al 2009; Myzak et al 2004)	

*limited references given, full list available in text

¹ Source² Botanical name

induced progressive demethylation of the *hTERT* promoter which allowed the E2F-1 repressor of *hTERT* to bind to its promoter and inhibit its expression (Berletch et al. 2008). Another classical example for EGCG-induced promoter demethylation inhibiting an oncogene is Wingless-type (Wnt) which occurs through epigenetic reactivation of Wnt inhibitory factor-1 (*WIF-1*) in lung cancer cells (Gao et al. 2009). The Wnt family consists of a group of signaling molecules that is extensively involved in developmental processes and oncogenesis. *WIF-1* is a Wnt antagonist that inhibits Wnt signaling by direct binding to Wnt molecules (Gao et al. 2009).

EGCG is unstable under physiological conditions, and methylation of EGCG by COMT is a modification that reduces the biological activity of EGCG (Landis-Piwowar et al. 2010). Recently, Moiseeva et al. (2007) showed that low-dose long-term exposure of bioactive components such as EGCG and genistein results in epigenetic alterations of gene expression, reduced growth, and increased cellular apoptosis in breast cancer cells. Furthermore, there are several synthetic analogs of EGCG that have been shown to have strong anti-cancer activity with more efficacy and stability than EGCG under physiological conditions (Kanwar et al. 2010; Huo et al. 2010; Landis-Piwowar et al. 2007). However, their epigenetic roles in cancer prevention and therapy have not yet been reported.

Although various studies have shown that green tea polyphenol or EGCG can effectively inhibit carcinogenesis in various animal organs (Tran et al. 2010; Liang et al. 2010; Sagara et al. 2010; Zhang et al. 2010), their epigenetic effects have been largely undetermined. Morey Kinney et al. (2009) demonstrated that administration of 0.3% green tea polyphenols (GTPs) to wild-type (WT) and transgenic adenocarcinoma of mouse prostate (TRAMP) mice showed no alteration in 5-methyl-deoxycytidine (5mdC) levels in prostate, gut, and liver from WT mice at both 12 and 24 weeks of age, with the single exception of a decrease of 5mdC in the liver at 12 weeks. Quite surprisingly, GTPs treatment did not inhibit tumor progression in TRAMP mice, although known pharmacodynamic markers of GTPs such as *Ssat* and *Clustrin* mRNA levels were altered in both WT and TRAMP prostates. However, Mittal et al. (2003) demonstrated that topical application of EGCG inhibits ultraviolet-B (UVB)-induced photocarcinogenesis by UVB-induced global DNA hypomethylation in SKH-1 hairless mouse model system. Both immunohistochemical analyses of 5mdC and DNMTs activities were restored significantly by topical application of EGCG in a chronic UVB-induced SKH-1 hairless mouse model system (Mittal et al. 2003). Studies have strongly correlated dietary habits and physical activity in relation to epigenetic reactivation of several genes, including tumor suppressor genes (Yuasa et al. 2009; Yun et al. 2010a). Yuasa et al. (2005) demonstrated in

primary gastric carcinoma patients that past life style and dietary habits including consumption of cruciferous vegetables and GTPs alter the methylation status of several genes such as *CDX2* and *BMP-2*, which are important for preventing gastric carcinogenesis. Recently, Volate et al. (2009) showed that administration 0.6% (w/v) GTPs in drinking water to azoxymethane-treated Apc Min/+ mice showed a significant decrease in CpG methylation in the retinoic X receptor alpha gene promoter leading to inhibition of intestinal tumorigenesis.

Histone modifications

The disruptions of histone acetylation/deacetylation balances by bioactive components through regulation of HAT and HDAC activities have received considerable attention in cancer prevention and therapy. In addition to DNA methylation inhibitory activity, EGCG also regulates gene expression through changes in histone modifications. Recently, Choi et al. (2009) discovered that EGCG has strong HAT inhibitory activity among all other catechins screened in various cell extracts from B lymphocytes, and the order of HAT inhibition by catechins is EGCG > EGC > EC. In the same study, it was discovered that EGCG abrogates p300-induced p65 acetylation in vitro and in vivo, increases the level of cytosolic I κ B α , and suppresses tumor necrosis factor α -induced NF- κ B activation. EGCG-induced p65 deacetylation events led to a cytoplasmic accumulation of I κ B α and subsequent cytosolic sequestration of NF- κ B resulting in the downstream inhibition of inflammatory genes such as *IL-6*, *COX-2*, and *NOS2* (Choi et al. 2009). Further, they found that EGCG does not make any significant changes in HDACs, HMTs, and SIRT1 in their assay system. However, studies with human prostate cancer LNCaP cells showed that exposure to 1–10 μ g/ml of GTPs for 1–7 days caused time-dependent inhibition of HDAC1-3 expression and increased the levels of acetylated histone H3 (LysH9/18) and H4 levels (Pandey et al. 2010). GTPs-induced histone acetylation and promoter demethylation reactivated the *GSTP1* gene, which is an important hallmark in prostate tumorigenesis.

Studies have also been initiated using combinations of GTPs with known HDAC inhibitors to enhance DNMT inhibition and HDAC inhibition activities, respectively, for effective chemoprevention (Nair et al. 2008). Recently, Nihal et al. (2010) showed that combined use of GTPs with vorinostat, known as SAHA, a HDAC inhibitor, imparts significant anti-proliferative effects against human melanoma cells. The demethylating activity of EGCG may synergize with the HDAC inhibitory action of vorinostat to help de-repress silenced tumor suppressor genes regulating key functions such as proliferation and cell survival. In keeping with this view, they showed a greater anti-melanoma

effect with the combination of EGCG and vorinostat than either agent alone (Nihal et al. 2010). There is very limited evidence regarding in vivo histone modification effects of GTPs. A study with dimethylaminoazobenzene-induced hepatocarcinogenesis in male Sprague–Dawley rats showed that administration of 0.05% (w/w) Polyphenon E (from black tea polyphenol) induced a significant decrease in HDAC1 expression compared to animals fed a control diet (Murugan et al. 2009).

Sulforaphane

Sulforaphane (SFN), an isothiocyanate naturally rich in widely consumed cruciferous vegetables such as broccoli, broccoli sprouts, cabbage, and kale, has been shown to reduce the risk of developing many common cancers (Higdon et al. 2007; Pledgie-Tracy et al. 2007; Keum et al. 2009; Cheung and Kong 2010). SFN mediates chemoprevention through several mechanisms including cell cycle arrest and induction of apoptosis and phase 2 detoxification enzymes (Bryant et al. 2010; Chu et al. 2009; Dinkova-Kostova et al. 2007; Bacon et al. 2003). However, there has been growing interest in epigenetic regulation by SFN in chemoprevention due to its histone deacetylase (HDAC) inhibition activity (Myzak et al. 2007; Dashwood and Ho 2007; Ho et al. 2009). The HDAC inhibition activity of SFN has been shown to lead to an increase in the global and local histone acetylation status of a number of genes (Bhamre et al. 2009; Telang et al. 2009; Dashwood and Ho 2008). SFN-mediated epigenetic alterations are believed to be strongly involved in the process of cancer chemoprevention by altering the expression of various genes, including tumor suppressor genes in various cancers (Herman-Antosiewicz et al. 2007).

SFN was found to inhibit DNMTs in MCF-7 and MDA-MB-231 breast cancer as well as CaCo-2 colon cancer cells (Meeran et al. 2010; Traka et al. 2005). Meeran et al. (2010) demonstrated that SFN treatment dose- and time-dependently inhibited human telomerase reverse transcriptase (*hTERT*), the catalytic regulatory subunit of telomerase, in both MCF-7 and MDA-MB-231 human breast cancer cells and that it had negligible effects on normal control cells. Further, DNA methyltransferases (DNMTs), especially DNMT1 and DNMT3a, were also decreased in SFN-treated breast cancer cells. More interestingly, down-regulation of DNMTs induced site-specific CpG demethylation occurring primarily in the first exon of the *hTERT* gene thereby facilitating CTCF binding associated with *hTERT* repression followed by cellular apoptosis in breast cancer cells (Meeran et al. 2010).

SFN has also been found to have HDAC inhibitory activity in many other cancer in vitro and in vivo cancer

models. SFN dose-dependently increased the activity of a beta-catenin-responsive reporter (TOPflash) and diminished HDAC activity in human embryonic kidney 293 cells (Myzak et al. 2004). In HCT116 human colorectal cancer cells, SFN inhibited HDAC activity thereby increasing histone acetylation at the p21^{WAF1/CIP1} promoter to enhance its expression (Myzak et al. 2004). Human prostate cancer BPH-1, LNCaP, and PC-3 cells also showed significant inhibition of HDAC activity by SFN treatment. Further, SFN-induced histone acetylation increased the expression of the p21^{WAF1/CIP1} protein, thereby inhibiting cell cycle arrest and inducing cellular apoptosis in these prostate cancer cell lines (Myzak et al. 2006b; Ho et al. 2009).

SFN also has HDAC inhibitory effects in vivo as shown in animal and human models. Myzak et al. (2006a) demonstrated that mice treated with a single oral dose of 10 μM SFN had significant HDAC inhibitory activity in colonic mucosa with increased acetylated histones H3 and H4. Further, the authors demonstrated that increased acetylation enhanced the expression of *p21^{WAF1/CIP1}* and *bax* gene expressions, thereby suppressing tumorigenesis in *Apc/+* mice (Myzak et al. 2006a). Another study demonstrated that administration of 7.5 μM SFN per animal for 21 days significantly reduced prostate cancer PC-3 tumor xenografts by inhibiting HDAC activity in vivo (Myzak et al. 2007). Importantly, in human subjects, a single dose of 68 g of broccoli sprouts inhibited HDAC activity significantly in peripheral blood mononuclear cells at 3 and 6 h following consumption (Myzak et al. 2007). Following oral dosing, sulforaphane metabolites were readily measurable in human breast tissue enriched for epithelial cells (Cornblatt et al. 2007). Collectively, SFN has been found to be a potent HDAC inhibitor both in vitro and in vivo models.

Genistein

Genistein is an isoflavone belonging to the flavonoids group of compounds and is found in a number of plants including fava beans, soybeans, lupin, kudzu, and psoralea. Genistein and other isoflavones have been found to have anti-cancer and anti-angiogenic properties in various cancers. Several studies have found moderate doses of genistein to have inhibitory effects on cancers of the prostate, cervix, brain, breast, and colon (Barnes 1995). It is becoming increasingly clear that genistein exerts multiple effects on cancer cell growth. Several mechanisms for the anti-proliferative and anti-cancer properties of genistein have been found, including prevention of DNA mutation, reduction in cancer cell proliferation, inhibition of angiogenesis, and induction of cellular apoptosis (Singh et al. 2006; Gu et al. 2005; Su et al. 2005; Sasamura et al. 2004). One potential

mechanism that has recently received considerable attention is that genistein is involved in regulation of gene transcription or silencing activity by modulating epigenetic events such as DNA methylation and/or chromatin modifications (Li and Tollefsbol 2010; Li et al. 2009a; Kikuno et al. 2008).

Several reports have found that genistein has DNA methyltransferase inhibitory activity as well as histone modification properties in cancer cells. In prostate cancer cells, genistein induced the expression of the tumor suppressor genes *p21^{WAF1/CIP1}* and *p16^{INK4a}* by altering promoter methylation and histone modification (Majid et al. 2008; Kikuno et al. 2008). Further, it was found that genistein increased acetylated histones 3 and 4 and H3-lysine4 at the *p21^{WAF1/CIP1}* and *p16^{INK4a}* transcription start sites, mediated by induction of HATs. Genistein-mediated promoter hypomethylation and hyperacetylation reactivate expression of tumor suppressor genes in human prostate cancer cells and are followed by cell cycle arrest and cellular apoptosis induced by cyclin and caspase pathways, respectively (Majid et al. 2008; Kikuno et al. 2008). This dietary bioactive compound also reactivates *BTG3*, a tumor suppressor gene, in A498, ACHN, and HEK-293 renal carcinoma cell lines (Majid et al. 2009). Genistein activates the epigenetic re-expression of *BTG3* by altering promoter DNA methylation through inhibition of DNMTs and methyl-CpG-binding domain 2 in these cells, whereas, genistein also increases histone acetylation by enhancing HAT activity, followed by enrichment of acetylated histones 3 and 4, dimethyl-H3K4, and trimethyl-H3K4 near the transcription start site at the *BTG3* gene promoter (Majid et al. 2009). This is consistent with other reports that genistein upregulated mRNA expression of the *BRAC1*, *p16^{INK4a}*, *RARB*, *MGMT*, and *p21^{WAF1/CIP1}* genes (Majid et al. 2008; Fang et al. 2005). Studies have also shown that genistein in combination with other DNA methyltransferases or HDAC inhibitors enhanced the reactivation of methylation-silenced genes (Raynal et al. 2008; Li et al. 2009a; Fang et al. 2005).

Genistein not only reactivates tumor suppressor genes through epigenetic modifications but also inhibits the expression of tumor promoter genes such as *hTERT*. Genistein inhibits DNMT1, DNMT3a, and DNMT3b and enriches inactivating histone trimethyl-H3K9 followed by transcriptional repression of *hTERT* expression in human breast cancer cells (Li et al. 2009a). In another study with MDA-MB-468 human breast cancer cells, low concentrations of genistein partially demethylated the *GSTP1* tumor suppressor gene promoter and reactivated its expression (King-Batoon et al. 2008).

In addition to in vitro epigenetic modulation, genistein-treated neonatal CD-1 mice showed anomalously hypomethylated *nucleosomal binding protein-1* promoter than hypermethylated control (non-genistein) treated mice (Tang et al. 2008). In contrast to genistein-induced DNA

hypomethylation mediated through DNMT inhibition, studies also have shown that genistein induced hypermethylation in some animal models (Day et al. 2002; Guerrero-Bosagna et al. 2008). In accordance with animal studies, genistein also increased hypermethylation in human studies randomized with selective cancer-related genes. Thirty-four healthy premenopausal women were randomized to take 40 or 140 mg isoflavones daily through one menstrual cycle, and the methylation status of *p16^{INK4a}*, *RASSF1A*, *RAR β 2*, *ER* and *CCND2* were assessed in intraductal specimens. The results showed that *RAR β 2* and *CCND2* were hypermethylated after genistein administration, and these results correlated well with serum genistein levels (Qin et al. 2009).

Curcumin

Curcumin, a yellow pigment present in the spice turmeric (*Curcuma longa*), has been linked with multiple beneficial activities including anti-inflammatory, anti-angiogenic and wound-healing, antioxidant, and anti-cancer properties. Curcumin has been shown in various animal models and human studies to be extremely safe even at very high doses; however, their solubility and bioavailability is an obstacle for therapeutic drug development (Aggarwal et al. 2003; Shishodia et al. 2007). Curcumin-mediated chemoprevention is mainly facilitated through cell cycle arrest and induction of cellular apoptosis in various cancer cells. Curcumin-induced apoptosis is involved with the intrinsic and extrinsic apoptosis pathways, the NF- κ B-mediated pathway as well as the PI3K/Akt signaling pathway (Reuter et al. 2008). Recent evidence has shown that curcumin also inhibits DNMT activities and histone modification such as HDAC inhibition in tumorigenesis (Fu and Kurzrock 2010).

Molecular docking of the interaction between curcumin and DNMT1 suggested that curcumin covalently blocks the catalytic thiolate of C1226 of DNMT1 to exert its inhibitory effect (Liu et al. 2005). This inhibition seems to be comparatively lower than other bioactive dietary components such as EGCG and genistein (Fang et al. 2007; Liu et al. 2005). Further, curcumin treatment with extracted genomic DNA from a leukemia cell line induced global hypomethylation (Liu et al. 2005). These results provide strong evidence that curcumin is a potent DNA hypomethylating agent, which is important for its broad-spectrum inhibitory activity in inflammation, cancer, and many other diseases.

Curcumin also has strong inhibitory activity against HDACs and HATs in several in vitro cancer models. Curcumin showed strong proliferation inhibition potency on Burkitt's lymphoma Raji cells in vitro, with the IC₅₀ value for 24 h at 25 μ M. Significant decreases in the

amounts of p300, HDAC1, HDAC3, and HDAC8 were detected after treatment with curcumin followed by prevention of I κ B α degradation and inhibition of nuclear translocation of the NF- κ B/p65 subunit (Chen et al. 2007; Liu et al. 2005). Meja et al. (2008) demonstrated that even very low concentrations of curcumin (30 and 200 nM) restored corticosteroid function in human monocytes exposed to oxidants. This occurred by maintaining HDAC2 activity via preventing oxidant-induced degradation of HDAC2 through down-regulating gene expression associated with protein degradation.

Curcumin has been identified as a strong inhibitor for HATs in both in vitro and in vivo cancer models. One of the early epigenetic studies showed that curcumin is a specific inhibitor of p300/CREB-binding protein (CBP) HAT activity but not of p300/CBP-associated factor, in vitro and in vivo. Curcumin-mediated p300/CBP inhibition was associated with repression of histones H3 and H4 and non-histone protein such as p53 and HIV-TAT proteins (Balasubramanyam et al. 2004). Another structural analysis study done by Marcu et al. (2006) revealed that alpha, beta unsaturated carbonyl groups in the curcumin side chain function as Michael reaction sites, which is required for its HAT inhibitory activity. Further, they demonstrate that curcumin selectively promotes proteasome-dependent degradation of p300 and closely related CBP protein without affecting the HATs such as PCAF or GCN5 in prostate PC3-M and peripheral blood lymphocytes. Interestingly, curcumin was able to effectively block histone hyperacetylation in both PC3-M prostate cancer cells and peripheral blood lymphocytes induced by the HDAC inhibitor MS-275 (Marcu et al. 2006).

Kang et al. (2006) showed a strong inhibition of curcumin-mediated HAT inhibitory activity associated with a decrease in histone H3 and H4 acetylation in brain cancer cells. Further, curcumin-induced histone modifications associated with caspases-mediated cellular apoptosis in brain cancer cells and enhanced neurogenesis, synaptogenesis, and migration of neural progenitor cells in brain-derived adult neural stem cells in vitro (Kang et al. 2006). Another study demonstrated that curcumin restored ultraviolet radiation-induced hyperacetylation in the promoter region of *ATF3*, *COX2*, and *MKP1*, which are inflammatory-related genes in human keratinocytes (Pollack et al. 2009). Further, studies have also shown that curcumin-mediated promoter hypoacetylation of certain genes was strongly correlated with gene silencing (Cui et al. 2007; Pollack et al. 2009). A very recent study showed that curcumin inhibits high glucose-induced proinflammatory cytokines by epigenetic modification in human monocytic (THP-1) cells. It was demonstrated that curcumin treatment significantly reduced HAT activity, p300 and acetylated CBP/p300 gene expression, and induced HDAC2 expression in THP-1 cells,

thereby inhibiting high glucose-induced proinflammatory cytokines, which is an important molecular target in reducing diabetic complications (Yun et al. 2010b).

In animal models, curcumin is found to be protective against cardiac failure, inflammation, and fibrosis through down-regulation of NF κ B, GATA4, and TGF β signaling as well as inhibition of HAT activity in rats (Morimoto et al. 2008; Li et al. 2008). Curcumin was also found to be very effective against streptozotocin-induced diabetes in male Sprague–Dawley rats through the inhibition of H3 hyperacetylation, NF κ B binding, and p300 and H3S10 phosphorylation (Chiu et al. 2009; Tikoo et al. 2008).

Resveratrol

Resveratrol is a dietary polyphenol derived from grapes, berries, peanuts, and other plant sources. Resveratrol was found to have strong anti-cancer properties by modulating signal transduction pathways that control cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis (Bishayee 2009). The anti-cancer property of resveratrol has been supported by its ability to inhibit proliferation of a wide variety of human tumor cells such as in skin, breast, prostate, lung, and colon (Mao et al. 2010; Vanamala et al. 2010; Liu et al. 2010; Kraft et al. 2009). These in vitro results have led to numerous preclinical animal studies to evaluate the potential of this drug for cancer chemoprevention and chemotherapy. Multiple biochemical and molecular actions seem to contribute to resveratrol effects against precancerous or cancer cells (Athar et al. 2009).

Resveratrol has been shown to have weaker DNMT inhibitory activity than other dietary bioactive components such as EGCG. Resveratrol prevents epigenetic silencing of BRCA-1 induced by aromatic hydrocarbon receptor (AHR) in MCF-7 human breast cancer cells (Papoutsis et al. 2010). It was demonstrated that AHR-mediated enrichment of mono-methylated-H3K9, DNMT1, and methyl-binding domain protein-2 at BRCA-1 promoter was restored, at least partially by resveratrol treatment, which was associated with BRAC-1 reactivation in MCF-7 cells (Papoutsis et al. 2010). In contrast, resveratrol did not significantly induce retinoic acid receptor beta 2 (RAR β 2) expressions by inhibiting RAR β 2 promoter methylation in MCF-7 cells compared to other adenosine analogs (Stefanska et al. 2010).

Studies have shown that resveratrol is associated with activation of the type III HDAC inhibitors, sirtuin 1 (SIRT1), and p300, in multiple in vitro and in vivo models (Kaeberlein et al. 2005). The activated SIRT1 negatively regulates Survivin expression through its deacetylase activity. Wang et al. (2008) found that human BRCA1-associated breast cancers have lower levels of SIRT1 expression. However, bioactive dietary components associated

with SIRT1 activation mediated an increased expression of human BRAC1 by altering H3 acetylation, which is an important strategy for targeted therapy for BRCA1-associated breast cancer (Wang et al. 2008). In addition, SIRT1-associated BRAC1 signaling is important for inhibiting tumorigenesis by activating oncoproteins in human breast cancer cells (Wang et al. 2008). It was shown in APC/+ mice that SIRT1-encoded proteins are required for resveratrol-mediated chemoprevention (Boily et al. 2009). SIRT1 also plays important roles in aging processes, since SIRT1-null mice could not tolerate caloric restriction and did not extend their lifespan compared to control mice (Boily et al. 2008).

Other bioactive components

In addition to the aforementioned bioactive components, other common fruits and vegetables have also been reported to have epigenetic targets either through DNMT inhibition or histone modifications. These bioactive compounds include apigenin (parsley), baicalein (Indian trumpet), cyanidins (grapes), isothiocyanate (cruciferous vegetables), rosmarinic acid (rosemary), and silymarin (milk thistle). All of these bioactive components have been reported to have either direct or indirect epigenetic targets in cancer chemoprevention and therapy (Davis and Ross 2007; Fang et al. 2007; Paluszczak et al. 2010; King-Batoon et al. 2008; Li and Tollefsbol 2010).

Conclusion and future directions

The emerging field of nutritional genomics targets nutrient-related genetic and epigenetic changes for prevention and therapy of various diseases including cancer. From the studies described herein, it is clear that bioactive dietary components hold great potential not only in the prevention but also in the therapy of a wide variety of cancers by altering various epigenetic modifications. Cancer is a multi-step processes and uses many survival pathways to prevail over normal cells. Therefore, bioactive components which have numerous molecular targets and suppress multiple cellular pathways such as EGCG may have strong potential for cancer prevention and treatment. Although individual bioactive components have shown great potential in prevention and treatment of various cancers, the combined use of dietary components should be more efficient in targeting the many cellular processes involved in tumorigenesis. Additional clinical studies are required to analyze the safety profile of doses, route of administration, organ specificity, and bioavailability of these bioactive components in human subjects. Ancient medicinal uses and extant scientific evidence strongly endorse the use of these bioactive

dietary components for drug discovery and development against cancer prevention and therapy.

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Conflict of interest The authors declare that they have no conflict of interest.

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