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## Epigenetic diet: impact on the epigenome and cancer

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### Abstract

A number of bioactive dietary components are of particular interest in the field of epigenetics. Many of these compounds display anticancer properties and may play a role in cancer prevention. Numerous studies suggest that a number of nutritional compounds have epigenetic targets in cancer cells. Importantly, emerging evidence strongly suggests that consumption of dietary agents can alter normal epigenetic states as well as reverse abnormal gene activation or silencing. Epigenetic modifications induced by bioactive dietary compounds are thought to be beneficial. Substantial evidence is mounting proclaiming that commonly consumed bioactive dietary factors act to modify the epigenome and may be incorporated into an ‘epigenetic diet’. Bioactive nutritional components of an epigenetic diet may be incorporated into one’s regular dietary regimen and used therapeutically for medicinal or chemopreventive purposes. This article will primarily focus on dietary factors that have been demonstrated to influence the epigenome and that may be used in conjunction with other cancer prevention and chemotherapeutic therapies.

### Keywords

acetylation; cancer; dietary; epigenetic; methylation; nutrigenomics

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Dietary factors have become agents of strong interest in the field of epigenetics. A number of bioactive dietary components that appear to have potential to prevent disease and promote

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overall health have been identified [1–4]. In fact, several naturally occurring dietary phytochemicals have been demonstrated to have anticarcinogenic properties and may play a role in regulating biological processes [5,6]. Many studies have shown that natural products have epigenetic targets in cancer cells and can act as cancer preventive agents. Compounds found in dietary phytochemical preparations such as teas, garlic, soy products, herbs, grapes and cruciferous vegetables are now generally accepted to defend against the development of many different types of tumors as well as acting as epigenetic modulators that impact not only the initiation, but also the progression of oncogenesis [6–9].

## Epigenetic mechanisms

The term epigenetics was coined in 1942 by developmental biologist Conrad H Waddington [10]. Epigenetics generally refers to heritable changes in gene expression and chromatin organization that are not due to alterations in the DNA sequence [11]. Epigenetic modifications typically occur by changes in DNA methylation, histone covalent modifications or by RNAi [12]. DNA methylation occurs when a methyl group is added to the 5-carbon (C<sup>5</sup>) position of a cytosine. The methylation of cytosine involves the transfer of a methyl group from *S*-adenosyl-L-methionine (SAM), a methyl precursor, to the cytosines in CpG dinucleotides [13]. DNA methylation has many roles in various cellular processes and may impact the transcription of genes by preventing the binding of key transcriptional factors [14–17]. Transcriptional silencing due to DNA methylation is thought to occur by the recruitment of methyl CpG-binding transcriptional repressors and by interfering with the DNA binding of transcriptional activators, which in turn results in a condensed chromatin state. In addition, methylated DNA may be bound by methyl-CpG-binding domain (MBD) proteins, which are essential for binding to 5-methylcytosine [16]. DNA methylation is catalyzed by enzymes known as DNA methyltransferases (DNMTs) and hypermethylation of CpG dinucleotides or CpG islands by DNMTs usually results in transcriptional gene silencing and gene inactivation [12]. The human genome contains four DNMT genes, *DNMT1*, *DNMT2*, *DNMT3A* and *DNMT3B* [18]. Altered DNMT expression and activity is seen in numerous diseases including autism, cardiovascular diseases, obesity, Type-2 diabetes and cancer [19–23]. In addition, global hypomethylation is associated with nearly all human cancers [24,25].

Histone modifications typically occur as post-translational modifications at the N-terminal of histones. These modifications include acetylation, methylation, phosphorylation, biotinylation and ubiquitination and are essential during development [26–28]. Histone modifications are catalyzed by enzymes such as histone methyltransferases (HMTs), histone demethylases (HDMs) histone acetyltransferases (HATs), and histone deacetylases (HDACs). HMTs act to add methyl groups to lysine and/or arginine residues in histones, while HDMs remove the methyl moieties. In turn, HATs catalyze the addition of acetyl groups to the lysine residues of histones, whereas HDACs are responsible for the removal of these groups [29,30]. Lysine methylation can cause either activation or repression of transcription, while arginine methylation typically activates transcription. Likewise, histone hyperacetylation results in the activation of normally repressed genes while hypoacetylation results in gene silencing. This is apparent in carcinogenesis where aberrant activity of HATs and HDACs are thought to trigger carcinogenic processes [31].

RNAi is the process by which dsRNA inhibits the accumulation of homologous transcripts from like genes [32]. RNAi or ncRNAs, in the form of antisense transcripts, can lead to transcriptional silencing by the formation of heterochromatin. The involvement of RNA in different silencing mechanisms has been described in detail in several organisms [33]. For example, in the yeast *Schizosaccharomyces pombe*, the deletion of different components of the RNAi machinery results in the loss of H3K9 methylation, as well as impairment of

centromere function [33,34]. Similarly, DNA methylation and H3K9 methylation have been demonstrated in *Arabidopsis thaliana* and in  $\alpha$ -thalassaemia [35,36]. RNAi has also been demonstrated to be involved in silencing genes associated with HIV-1, along with several types of cancers [37–41]. In addition, noncoding miRNAs can control the expression of DNMTs and other enzymes associated with epigenetic modifications, which affect mRNA translation and stability [42–44]. Exciting developments have indicated that RNAi-directed silencing of heterochromatic regions might trigger direct histone modifications and DNA methylation to specific loci, causing gene silencing [35,36,45,46].

Epigenetic modifications are of particular interest in the field of cancer research since their impact on the epigenome is involved in cell proliferation, differentiation and survival [27,47,48]. Furthermore, epigenetic modifications are often involved in transcriptional regulation and have been implicated both in tumor development and progression [40,49,50]. Epigenetic modifications causing transcriptional deregulation may result in the inappropriate expression or activation of transcription factors associated with oncogenes and/or the failure to express genes responsible for tumor suppression [51]. In fact, cancer cells have genome-wide aberrations in a number of epigenetic markers, including global hypomethylation, global downregulation of miRNAs, promoter-specific hypermethylation, histone deacetylation and upregulation of epigenetic machinery [52]. In addition, the impact of epigenomic processes in cancer is apparent by the finding that at least half of all tumor suppressor genes are inactivated through epigenetic mechanisms in tumorigenesis [16,53–55]. Bioactive dietary components consumed by ingesting natural products including fruits and vegetables can act as sources of vitamins and minerals. While this is an invaluable role, these agents have high potential for application to oncogenesis owing to in part to their anticarcinogenic properties [9,56]. A growing body of evidence suggests that dietary agents as well as non-nutrient components of fruits and vegetables can affect epigenetic processes and are involved in processes, including the reactivation of tumor suppressor genes, the initiation of apoptosis, the repression of cancer-related genes and the activation of cell survival proteins in different cancers [57–60]. Dietary phytochemicals such as tea polyphenols, genistein, sulforaphane (SFN), resveratrol, curcumin and others have been demonstrated to be effective agents against cancer and to act through epigenetic mechanisms that affect the epigenome [56,61].

## Epigenetic diet phytochemicals affecting the epigenome

Dietary factors play a role in many normal biological processes and are also involved in the regulation of pathological progressions. Diseases linked to genetic and epigenetic modifications can be influenced by environmental and dietary factors. In particular, nutritional factors, drugs, chemicals used in pesticides, environmental compounds and inorganic contaminants (i.e., arsenic) can alter the epigenome, and may contribute to the development of abnormalities [62–66]. It has become increasingly clear that environmentally induced epigenetic changes can be mediated, in part, by diet [67–69]. This is especially illustrated by an early investigation conducted in an animal model, which demonstrated that dietary methyl deficiency of folate, choline and methionine altered DNA methylation patterns in the liver and induced hepatocarcinoma [70]. Evidence has also emerged indicating that giving mice that have developed methyl-deficiency-induced hepatocarcinoma a methyl-sufficient diet can lessen the occurrence of abnormal DNA methylation [71]. Because epigenetic variation can be influenced by dietary factors, it is reasonable to believe that investigating strategies that utilize dietary compounds to target epigenetic modifications may be worthwhile in preventing and treating diseases including cancer.

## Dietary polyphenols

Polyphenols are present in fruits and vegetables and are a vital part of the human diet [56,72]. Plant polyphenols can be divided into at least ten different classes based on their chemical structure. These classes include: flavonoids, stilbenes, phenolic acids, benzoquinones, acetophenones, lignins and xanthenes [72,73]. Polyphenols can range from simple molecules to highly complex compounds and are derived from either phenylalanine (a phenol intermediate) or its precursor shikimic acid. They typically contain one or more sugar residues linked to a hydroxyl group and occur in a conjugated form [72]. Some estimate that more than 8000 distinct dietary polyphenols exist [72]. Examples of common polyphenols include (–)-epigallocatechin-3-gallate (EGCG; found in green tea), curcumin (found in curry) and resveratrol (found in grapes). These dietary polyphenols have a protective role against diseases and also have a significant impact on cancer prevention [74,75]. In fact, various mechanisms have been identified that help to explain the preventive nature of polyphenols, including their ability to alter the epigenome in cancer cells by chromatin remodeling or by reactivating silenced genes [76–78]. The chemo-preventative potential of dietary polyphenols can be traced to their ability to inhibit DNMTs as well as their ability to act as histone modifiers. Both of these properties of dietary polyphenols can significantly change the epigenome of cancer cells and are viewed as attractive possibilities for anticancer therapeutics.

## Tea polyphenols

Next to water, tea is the most consumed beverage worldwide with approximately 20 billion cups consumed daily [79]. The three most popular types of tea (green, black and oolong) are differentiated based on the degree of fermentation they undergo. Green tea leaves are dried and roasted but not fermented, whereas black tea leaves are well fermented and oolong tea leaves are only partially fermented [79,80]. Studies have indicated that compounds present in tea may reduce the risk of diseases including cancer. Teas contain polyphenolic compounds that serve to protect plants from photosynthetic stressors, reactive oxygen species and consumption by herbivores [56]. As previously stated, polyphenolic compounds in tea may actively reduce the risk of diseases such as cancer. One subcategory of polyphenols, catechins, is the most abundant of the bioactive compounds in green tea. These include (–)-epicatechin (EC), (–)-epicatechin-3-gallate (ECG), (–)-epigallocatechin (EGC), and EGCG [81]. While all of the aforementioned catechins have been found to share similar properties, the most efficient of these compounds in targeting factors like DNMTs is EGCG [77,78]. EGCG accounts for more than 50% of the active compounds in green tea and has been extensively studied for its anticarcinogenic properties [82]. While studies conducted by Chuang *et al.* report disagreeing results regarding the effects of EGCG on DNA methylation [83], an increasing number of investigations have suggested a positive correlation between the consumption of EGCG and the inhibition of oral, breast, prostate, gastric, ovarian, esophageal, skin, colorectal, pancreatic, and head and neck cancers [83–88].

Epigallocatechin-3-gallate is thought to exert its anticancer effects through several different mechanisms much of which can be altered by epigenetic mechanisms; these include the induction of apoptosis and cell cycle arrest, inhibition of oxidative stress and angiogenesis, regulation of signal transduction and reduction of cancer cell proliferation [89–92]. EGCG can inhibit DNMT activity through direct enzyme interaction leading to demethylation and reactivation of genes previously silenced by methylation (see Figure 1 & Table 1) [77,93,94]. Early studies conducted by Fang *et al.* demonstrated that treatment of esophageal cancer cells with EGCG in fact lowered DNMT activity and caused a time- and dose-dependent reversal of hypermethylation in tumor suppressor genes including *p16*, *RARβ*, *hMLH1* and *MGMT* [95]. A recent investigation involving A431 skin cancer cells revealed that EGCG treatment not only decreased global DNA methylation levels, but also decreased

the levels of 5-methyl-cytosine, DNMT activity, mRNA and protein levels of DNMT1, DNMT3a and DNMT3b resulting in the re-expression of p16(INK4a) and p21/Cip1 mRNA and proteins [96]. In addition, in studies conducted by Li *et al.* it was found that EGCG is capable of reactivating estrogen receptor- $\alpha$  (ER- $\alpha$ ) expression in ER $\alpha$ -negative MDA-MB-231 breast cancer cells [97]. This is of particular importance in breast cancer therapeutics where many treatment options utilize the ER pathway. Moreover, studies conducted by Berletch *et al.* indicated that EGCG treatment of MCF-7 breast cancer cells resulted in downregulation of the *hTERT* gene and a time dependent decrease in *hTERT* promoter methylation, which paradoxically leads to a decrease in telomerase activity in these cells [93]. In addition, EGCG has been demonstrated to demethylate the *Wnt* oncogene promoter in lung cells [98]. EGCG can also partially reverse the hypermethylation status of the *RECK* tumor suppressor gene in oral carcinoma cells, significantly enhancing the expression of RECK mRNA [99]. Moreover, treatment of LNCaP human prostate cancer cells with green tea polyphenol caused a time- and dose-dependent re-expression of GSTP1, whose overexpression has been associated with the development of several types of cancer [100]. In addition, Choi *et al.* have identified EGCG as a HAT inhibitor with global specificity for the majority of HAT enzymes [101]. Recently, EGCG has also been found to modulate miRNA expression in hepatocellular carcinoma cells (Figure 2 & Table 1) [102]. Furthermore, either EGCG or green tea polyphenols can inhibit carcinogenesis based on numerous *in vivo* studies; however, the effects on epigenetic mechanisms and the epigenome *in vivo* have not yet been clearly defined [103–105].

While considerable evidence has been presented showing the anticarcinogenic properties of green tea consumption, the EGCG compound is unstable under normal physiological conditions. To this end, synthetic analogs of EGCG have been studied in physiological conditions and show strong anticancer activity with more stability and efficacy [106]. Interestingly, studies conducted using EGCG and a prodrug of EGCG (pEGCG and EGCG octa-acetate) to enhance the bioavailability and stability of EGCG display inhibition of hTERT, the catalytic subunit of telomerase, through epigenetic mechanisms affecting the *hTERT* gene regulatory region in breast cancer cells [107,108]. Studies provide evidence that EGCG alone or combined with other epigenetic-modifying compounds such as HDAC inhibitors may be effective as cancer therapeutic agents and these lines of investigation are currently of considerable interest in the field of epi-genetics and in the development of an epigenetic diet for the purpose of cancer prevention.

## Resveratrol

The dietary polyphenol resveratrol is naturally found in several plants including peanuts, mulberries, cranberries and blueberries, but is most abundant in the skin of grapes [109]. Resveratrol is also consumed in the form of red wine. Antioxidant, anti-inflammatory and anti-cancer properties of resveratrol occur through various molecular and biochemical pathways [110,111]. For instance, resveratrol has an impact on signaling pathways that control cell division, cell growth, apoptosis, angiogenesis and tumor metastasis [112–114]. Antiproliferative properties of resveratrol have been reported in liver, skin, breast, prostate, lung and colon cancer cells [115–117]. It has also been demonstrated that colon carcinoma cells treated with resveratrol inhibits cell migration, adhesion and invasion [118]. The beneficial effects of resveratrol have also been demonstrated *in vivo* in that this bio-active dietary component has been reported to reduce adenocarcinoma cell metastases in BALB/c mice thereby increasing the percentage survival of the mice [119,120].

While resveratrol has potential as a dietary anticancer agent, it displays less DNMT inhibitory activity than some of its dietary counterparts including EGCG (Figure 1 & Table 1). However, resveratrol is capable of preventing the epigenetic silencing of the BRCA1 tumor suppressor protein [121] and Papoutsis *et al.* demonstrated that resveratrol-treated

MCF-7 cells partially restored monomethylated-H3K9, DNMT1, and MBD2 at the BRCA1 promoter [121]. Inhibition of DNMT has been shown in nuclear extracts from MCF-7 breast cancer cells treated with resveratrol although resveratrol was unable to reverse the methylation of certain tumor suppressor genes [60]. In addition, resveratrol was unable to inhibit *RARβ2* and *MGMT* promoter methylation in MCF-7 cells [122,123].

Importantly, resveratrol is associated with activating SIRT-1 and p300, which are known HDAC inhibitors [124]. As aforementioned, HDACs are responsible for removing acetyl groups from the lysine residues of histones. There are to date at least 18 HDAC isozymes that are divided into different classes. Several studies have reported a link between class I HDACs and the development of malignant tumors, while this link has been observed substantially less in class II HDACs [125]. Class III HDACs are homologous to the Sir2 protein in yeast and are collectively known as Sir proteins or sirtuins. Sirtuins have specific inhibitors and are not responsive to class I and II HDAC inhibitors [126]. The SIRT-1-encoded proteins are necessary for chemoprevention mediated by resveratrol [127]. It is believed that resveratrol activates SIRT-1 by mimicking physiological pathways that stimulate SIRT-1 [128,129]. The activation of SIRT-1 by resveratrol negatively regulates expression of the antiapoptotic protein, Survivin, by deacetylating H3K9 within the promoter of its gene [130,131]. In addition, studies conducted by Wang *et al.* found that SIRT-1 mediates BRCA1 signaling in human breast cancer cells by altering H3 acetylation [130]. Furthermore, treatment of prostate cancer cells with resveratrol demonstrates enhanced p53 acetylation and apoptosis by inhibition of the MTA–NuRD complex [132]. In terms of aging, resveratrol has also been reported to extend the lifespan and improve the health of mice on a high-calorie diet [133]. Sirturins typically exhibit their activity through deacetylation of nonhistone proteins but are also important in the maintenance of histone acetylation patterns [126,134]. This evidence suggests that sirturins can affect normal gene expression through chromatin regulation and may provide a link between epigenetic changes associated with aging and obesity as well as epigenetic modifications in tumors.

## Curcumin

Curcumin, a diferuloylmethane, is a polyphenol that originates from the plant, *Curcuma longa*. Curcumin is the main component of the spice turmeric and is responsible for the yellow pigmentation of curry. This bioactive dietary component appears to have anti-inflammatory, antioxidant, antiangiogenic and anti-cancer properties and is used as a therapeutic agent in Indian and Chinese medicine [135,136]. Investigations indicate that curcumin inhibits DNMT activity (Figure 1 & Table 1) by covalently blocking the catalytic thiolate of C1226 of DNMT1 [137,138]. Moreover, there is evidence that curcumin may be an effective DNA hypomethylating agent that could facilitate the expression of inactive prometastatic and proto-oncogenes [16,77,137,139]. Curcumin also has epigenomic effects in that genomic DNA from leukemia cells show global hypomethylation after curcumin treatments [140]. In addition, studies conducted by Valinluck and Sowers indicated that curcumin induced anti-inflammatory effects. These effects stemmed from halogenated cytosine products that mimic 5-methylcytosine in DNA methylation. These data provide evidence of a link between inflammation and epigenetic alterations that are also seen in cancer [141].

Curcumin also functions as a histone modifying compound and as a HDAC and HAT inhibitor (Figure 3 & Table 1) [142]. While this inhibition is less than that of some other dietary epigenetic modifiers, Kang *et al.* found that the inhibition of curcumin-mediated HAT activity results in a decrease in global histone H3 and H4 acetylation in brain cells [142]. Furthermore, independent studies conducted by Cui and Pollack demonstrated that promoter hypoacetylation of several histones was curcumin-mediated and correlated to gene silencing [143,144]. In addition, numerous animal studies have built upon *in vitro*

investigations and support the ability of curcumin to inhibit HATs and HDACs in several disease models including tumorigenesis [77,139,142,145–148]. While the inhibition of both HATs and HDACs may seem contradictory, recent investigations provide evidence that HAT inhibitors have a potential role in cancer therapies and that inhibition of both HATs and HDACs together may provide a potent strategy for cancer treatment [149]. Chemoprevention mediated by curcumin is mainly facilitated by the NF- $\kappa$ B and PI3K/AKT signaling pathway and typically induces cell cycle arrest and apoptosis [150]. Several groups have shown that curcumin is a potent inhibitor of p300/CBP activity in leukemia, hepatoma and cervical cancer cellular extracts [151,152]. There are also indications that curcumin prevents histone hyperacetylation induced by the MS-275 HDAC inhibitor in peripheral blood lymphocytes and cancer cells [151,153]. In addition, curcumin has been found to alter the miRNA expression profile in pancreatic cancer cell lines (Figure 2 & Table 1) [154,155].

The data showing the strong inhibitory activity of curcumin in carcinogenesis suggests its therapeutic abilities in cancer or its use in chemoprevention. An issue with using curcumin as a bioactive agent is that its insolubility and instability in water leads to low bioavailability. However, the bioavailability of curcumin can be enhanced by utilizing properties of dietary factors such as rubusoside (found in Chinese blackberry extract) and molecular compounds such as phosphatidylcholine (found in soy and egg yolks) thereby increasing its potential in cancer chemoprevention or therapy [156,157].

### Isoflavones (genistein)

Isoflavones belong to the flavonoid group of compounds, the largest class of polyphenolic compounds [158]. Isoflavones are found in a number of plants including soybeans, fava beans and kudzu. Several isoflavones have been investigated and indications are that they have anti-angiogenic and anticancer properties. Genistein, a phytoestrogen primarily found in soybeans, is perhaps the most studied of these bioactive compounds. This estrogen-like compounds acts as a chemopreventative agent in several types of cancers [159]. In fact, moderate doses of genistein appear to induce inhibitory effects on cervical, prostate, colon and esophageal cancers [160–162]. Several mechanisms have been found to contribute to the anticarcinogenic properties of genistein including its ability to regulate gene transcription by affecting histone acetylation and/or DNA methylation [163].

Genistein treatment of esophageal squamous cell carcinoma partially reversed DNA hypermethylation and reactivated *p16*, *RAR $\beta$*  and *MGMT* and a similar reversal was also seen in prostate cancer cells [162]. Further studies conducted in prostate cells indicate that genistein induces the expression of the tumor suppressor genes *p16* and *p21* by altering histone and promoter methylation [164,165]. Likewise, studies using breast cancer cells treated with a low (3.125  $\mu$ M) concentration of genistein demethylated the promoter of the *GSTP1* gene [166]. In addition, genistein-treated prostate and renal cells showed a reversal of hypermethylation of the *BTG3* gene, a known tumor suppressor [167,168]. Moreover, genistein combined with DNA methylation inhibitors or other DNMTs can enhance the reactivation of genes silenced by methylation [163,169]. As evidence of this, Li *et al.* found that genistein inhibits DNMT1, 3a and 3b (Figure 1) and inhibits the expression of hTERT. Genistein also increases acetylation by enhancing HAT activity (Figure 3) [168]. Furthermore, investigations have demonstrated that genistein-mediated hypomethylation and hyperacetylation reactivate the expression of tumor suppressor genes in prostate cancer cells [164,165]. Genistein and other isoflavones have also been found to regulate miRNA expression in several cancer cell lines (Figure 2 & Table 1) [170,171].

Importantly, the effects of genistein have recently been tested in humans. For instance, in studies conducted by Qin *et al.*, 34 healthy premenopausal women received either 40 mg or 140 mg of isoflavones, including genistein, daily through one menstrual cycle. Methylation

assessment of five genes known to be methylated in breast cancer (*p16*, *RASS1FA*, *RAR $\beta$ 2*, *ER* and *CCND2*) was conducted on intraductal samples. The findings revealed hypermethylation (which typically leads to gene silencing) of cancer-related genes *RAR $\beta$ 2* and *CCND2* was increased after genistein treatment and correlated with serum genistein levels [172].

### Isothiocyanates

Isothiocyanates are a category of dietary compounds present in cruciferous vegetables including broccoli, cabbage and kale. Isothiocyanates are characterized by a sulfur containing functional group (N=C=S). Commonly used isothiocyanates include: allyl isothiocyanate (AITC), benzyl isothiocyanate (BITC), phenethyl isothiocyanate (PEITC) and SFN [173]. Reports have indicated that isothiocyanates have proapoptotic and antiproliferative properties [174]. Several investigations have demonstrated evidence that isothiocyanates, including iberin, SFN and a SFN analog erucin, inhibit cancer cell growth and exhibit proapoptotic capabilities [174]. Treatment with isothiocyanates has also been reported to prevent esophageal tumorigenesis in rats [175]. Isothiocyanates are known to affect the epigenome and have anti-cancer properties. In fact, allyl-isothiocyanate, found in broccoli, has been reported to increase histone acetylation in mouse erythroleukemia cells. Phenylhexyl isothiocyanate (PHI), a synthetic isothiocyanate, acts as a HDAC inhibitor and has been demonstrated to hypomethylate *p16* and to induce histone H3 hyperacetylation in myeloma cells [176]. PHI has also been reported to inhibit HDAC activity and plays a role in remodeling chromatin to activate *p21* and induce cell cycle arrest in prostate cancer and leukemia cells [177,178]. In addition, prostate cancer cells treated with PEITC, found in watercress, demonstrated demethylation and re-expression of the *GSTP1* gene [179].

One of the main isothiocyanate compounds is SFN. SFN is an isothiocyanate found in cruciferous vegetables such as broccoli. Investigations into the effects of dietary SFN have shown its anticarcinogenic activity in several cancers [173,180–182]. SFN has many effects that include inducing apoptosis, affecting the cell cycle and acting as a HDAC inhibitor (Figure 3 & Table 1). SFN-initiated HDAC inhibition has been found to have epigenomic effects in that it can increase global and local histone acetylation of a number of genes and is thought to be involved in the regulation of cancer-related genes [183–185]. Studies conducted in colorectal and prostate cancer cells show inhibition of HDAC activity due to SFN treatments. In addition, studies conducted by Myzak *et al.* using human subjects demonstrated that a dose of 68 g of broccoli sprouts was effective in inhibiting HDAC activity in peripheral blood mononucleocytes [186]. In addition, studies conducted by Meeran *et al.* indicated that SFN can inhibit DNMTs in breast cancer cells and that SFN inhibits hTERT in a dose and time-dependent manner [59]. This finding is significant since hTERT is overexpressed in approximately 90% of cancers.

### Other dietary compounds affecting the epigenome

Selenium (Se) is a nutrient found in Brazil nuts, chicken, game meat and beef [187]. Other chemical forms of Se include selenomethionine, selenocysteine, selenate and selenite. Se is an essential element with antioxidant, proapoptotic, DNA repair and anticancer properties [188–190]. Se is vital for human health and Se deficiencies have been linked to various human diseases including cancer [191]. In addition, several other selenoproteins (i.e., selenium binding protein-1) have been indicated as important in the development of cancers; however, their epigenetic effects have not been clearly defined [192].

In trials designed to test Se in nonmelanoma skin cancers, 1312 individuals at a high risk of developing this disease were given either 200  $\mu$ g of Se or placebo orally per day for an average of 4.5 years [193,194]. This trial did not prevent skin cancer but did produce a



significant 44% secondary decrease in lung cancer incidence [193]. Se has been linked to DNA methylation in cellular and animal models and Xiang *et al.* found that Se treatments caused partial promoter DNA demethylation and re-expression of GSTP1 in prostate cancer cells. This study also demonstrated that Se decreased histone deacetylase activity (Figure 3 & Table 1) and increased levels of acetylated H3K9, and decreased levels of methylated H3K9 [191]. In animal studies rats fed with selenium-rich diets induced significant DNA hypomethylation in the liver and colon [195,196]. Furthermore, Se deficiency has been demonstrated to cause global hypomethylation and promoter methylation of the *p16* and *p53* tumor suppressor genes [197]. Se can also decrease DNMT1 protein expression and inhibit DNMT1 (Figure 1 & Table 1) by direct interaction and indirectly by influencing homocysteine concentrations [198]. In addition, investigations have demonstrated that treatment of prostate cancer cells with selenite, an inorganic form of Se, can restore the expression of anticancer genes silenced by hypermethylation suggesting that epigenetic regulation by Se may play a role in cancer prevention [191]. Although these studies are intriguing, further studies involving the epigenetic influence of selenium are needed to fully appreciate the impact of selenium on the epigenome.

Garlic (*Allium sativum*) has been used for the prevention of disease for many years, and is thought to have antibacterial, antiviral and anti-inflammatory activities [199]. Garlic cloves contain several compounds including: vitamins A, B-complex, C, E, fiber, free amino acids, sulfur/organosulfur compounds and proteins. In addition, garlic also contains small amounts of selenium that may contribute to its chemopreventive properties. Garlic extracts and compounds have been used in experiments involving cancer treatment and prevention in isolated cell systems and in *in vivo* models [199]. These studies have shown that garlic acts to inhibit cell cycle progression, induce apoptosis, inhibit angiogenesis and modifies histones [200]. Studies conducted by Nian *et al.* revealed that garlic organosulfur compound, allyl mercaptan, inhibits histone deacetylase (Figure 3 & Table 1) and enhances Sp3 binding on the P21/WAF1 promoter, which results in elevated p21 protein expression and cell cycle arrest [200,201]. In addition, investigations conducted by Lea *et al.* demonstrate the induction of histone acetylation in cancer cells treated with garlic compounds [202,203].

Folic acid, or folate, is a B vitamin found in many beans, grains, fortified breakfast cereals, pastas and green vegetables. Folate is a key element in the methyl-metabolism pathway. Dietary methyl deficiency can alter hepatic DNA methylation patterns and induce liver cancer (Table 1) [70,71]. While folate has been studied extensively for its developmental effects, folate deficiencies lead to hypomethylated genomic DNA, which is associated with tumorigenesis [204,205]. Folate deficiencies are reported to contribute to the development of several different cancers including: breast, cervix, ovary, brain, lung and colorectal [206–208]. Folate regulates the biosynthesis, repair and methylation of DNA, whereas deficiencies in folate can induce carcinogenesis by augmenting these processes [207]. In addition, studies involving colorectal cancer indicated that folate deficiency can alter cytosine methylation in DNA leading to the activation of *c-Myc*, a known oncogene [209,210].

While most natural dietary products have shown beneficial effects on the epigenome, not all dietary components share this characteristic. In fact, alcohol consumption is associated with harmful epigenetic modifications as well as the development/progression of several human cancers. For example, colorectal cancer patients with high alcohol consumption had a prevalence of promoter hypermethylation of numerous genes when compared with patients with low alcohol consumption (Table 1) [211,212]. In addition, studies involving head and neck cancers demonstrated that promoter hypermethylation of *MGMT* and WNT pathway regulators occurred more frequently in heavy and light drinkers than in nondrinkers [213].

Other dietary factors including those found in coffee, cashews, tomatoes, parsley, milk thistle and rosemary, have also been reported to have epigenetic targets all of which could not be mentioned in this article. However, bioactive components of these nutrients may be of considerable interest and may have epigenetic targets in cancer [123,214–217].

## Future perspective

Different mechanisms are involved in the maintenance of epigenetic states. Studies discussed herein have shown that dietary factors are likely to contribute to epigenetic alterations and in some cases may be able to reverse abnormal epigenetic states. In addition, while many of the aforementioned studies were conducted using a particular dietary factor, it is reasonable to believe that most may be consumed in combination and over a period of a lifetime. This may provide a rationale for studying nutrient epigenetic modifiers more in combination studies or the proposal of an ‘epigenetic diet’ focused on consuming products that show the ability to stimulate beneficial epigenetic modifications, including increased consumption of fruit, vegetables and those dietary components that are mentioned herein. This may be used from a chemopreventive standpoint to incorporate anticancer nutrients into one’s daily routine to impede disease mechanisms. From a therapeutic perspective many nutrients have been and are being studied for their ability to prevent and reduce the risk or severity of certain diseases and for their anticarcinogenic properties. The field of nutrigenomics involves studying how genes and dietary components interact to influence phenotype and can reveal how one responds to bioactive components based on genetics, nutrient-induced changes in DNA methylation and chromatin alterations, and nutrient-induced changes in gene expression, whereas the field of nutriepigenomics involves the lifelong remodeling of our epigenomes by nutritional factors [218–220]. Nutriepigenomic studies focusing on individual responses to bioactive components and individualized epigenetic diets consisting of bioactive dietary factors mentioned herein will be of particular interest in the future. Furthermore, future studies focusing on the clinical relevance and mechanism of epigenetic modification of bio-active dietary factors are needed to further assess the applicability of dietary factors as cancer preventive and chemopreventive agents.

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## Executive summary

### Epigenetic mechanisms

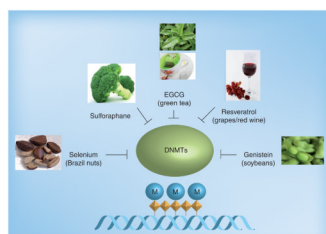
- Epigenetic modifications typically occur by changes in DNA methylation, histone modifications, or by RNAi and can be influenced by dietary factors.
- At least a half of all tumor suppressor genes are inactivated through epigenetic mechanisms in tumorigenesis.
- Evidence suggests that dietary agents can affect epigenetic processes.

### Epigenetic diet compounds

- Dietary polyphenols such as tea polyphenols (i.e., epicatechin, epicatechin-3-gallate, epigallocatechin and epigallocatechin-3-gallate), resveratrol and curcumin can inhibit DNA methyltransferases and act as histone modifiers and demonstrate potential as anticancer therapeutic as well as chemopreventive agents.
- Isoflavones such as genistein are found in soybeans, fava beans and kudzu and have been demonstrated to have anticancer properties that, in part, involve DNA methylation.
- Isothiocyanates including sulforaphane are known to affect the epigenome and to have anticancer properties and act as a histone deacetylase inhibitor.
- Other dietary factors including those found in Brazilian nuts, chicken, cereals, coffee, cashews, garlic, parsley, milk thistle and rosemary, have also been reported to have epigenetic targets in cancer. While most natural dietary products have shown beneficial effects on the epigenome, some dietary components (i.e., alcohol) are associated with harmful epigenetic modifications.

### Future perspective

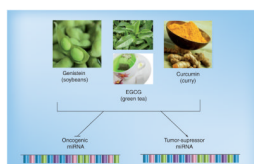
- Many nutrients have been and are being studied for their chemopreventive and/or chemotherapeutic properties.
- Numerous investigations provide a rationale for studying nutrient epigenetic modifiers further in combination studies. Furthermore, the proposal of an 'epigenetic diet' focused on consuming products that show the ability to stimulate beneficial epigenetic modifications will be of particular interest in the future.



**Figure 1. Dietary inhibitors of DNA methyltransferases**

DNMTs catalyze DNA methylation by adding a methyl group (CH<sub>3</sub>; indicated by M) to cytosines of CpG dinucleotides (diamond shapes). Hypermethylation of CpG dinucleotides or CpG islands by DNMTs usually results in transcriptional gene silencing and gene inactivation. Several bioactive compounds found in foods (e.g., EGCG in green tea) act as dietary inhibitors of DNA methyltransferases and also alter gene expression via epigenetic mechanisms.

DNMTs: DNA methyltransferases; EGCG: Epigallocatechin-3-gallate; M: Methylation.

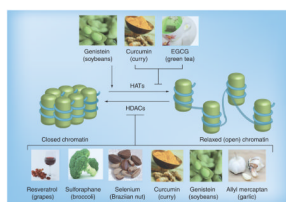


**Figure 2. Dietary effectors of miRNAs**

miRNAs serve as regulators of gene expression. Evidence has been reported supporting the fact that dietary agents target the miRNA of oncogenes and/or tumor suppressors and impact the expression level of miRNAs.

EGCG: Epigallocatechin-3-gallate.





### Figure 3. Dietary modifiers of histones

Bioactive compounds including resveratrol, sulforaphane and curcumin have the ability to alter (indicated by cylinders) HATs as well as HDACs. These histone modifications cause conformational changes in chromatin structure that lead to changes in DNA accessibility. HATs induce a relaxed chromatin state allowing transcriptional factors access to DNA (blue cords) and activate gene expression whereas chromatin in its closed state is indicative of gene silencing and repression. Dietary compounds can inhibit and/or enhance (arrow) HATs and HDACs thereby altering gene expression.

EGCG: Epigallocatechin-3-gallate; HAT: Histone acetyltransferase; HDAC: Histone deacetylase.

**Table 1**

Bioactive epigenetic diet compounds, food sources and epigenetic functions.

Epigenetic diet compounds	Food sources	Epigenetic functions
EC, ECG, EGC and EGCG	Green tea	DNMT and HAT inhibitor, modulates miRNA
Resveratrol	Grapes, peanuts, mulberries, cranberries, blueberries	DNMT and HDAC inhibitor
Curcumin	Tumeric, curry	DNMT inhibitor and miRNA modulator
Genistein	Soybeans, fava beans	DNMT and HDAC inhibitor, enhances HATs, modulates miRNA
Isothiocyanates, sulforaphane	Broccoli, cabbage, kale, watercress	DNMT and HDAC inhibitor
Selenium	Brazilian nuts, chicken, game meat, beef	DNMT and HDAC inhibitor
Allyl mercaptan, organosulfur compounds	Garlic	HDAC inhibitor
Folate	Beans, grains, fortified breakfast cereals, pastas, green vegetables	Deficiencies alter DNA methylation patterns
Alcohol	Alcoholic beverages	High consumption increases promoter hypermethylation

DNMT: DNA methyltransferase; EC: Epicatechin; ECG: Epicatechin-3-gallate; EGC: Epigallocatechin; EGCG: Epigallocatechin-3-gallate; HAT: Histone acetyltransferase; HDAC: Histone deacetylase.