Published in final edited form as:

Semin Cancer Biol. 2016 October ; 40-41: 82–99. doi:10.1016/j.semcancer.2016.04.002.

Dietary phytochemicals as epigenetic modifiers in cancer: Promise and challenges

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Abstract

The influence of diet and environment on human health has been known since ages. Plant-derived natural bioactive compounds (phytochemicals) have acquired an important role in human diet as potent antioxidants and cancer chemopreventive agents. In past few decades, the role of epigenetic alterations such as DNA methylation, histone modifications and non-coding RNAs in the regulation of mammalian genome have been comprehensively addressed. Although the effects of dietary phytochemicals on gene expression and signaling pathways have been widely studied in cancer, the impact of these dietary compounds on mammalian epigenome is rapidly emerging. The present review outlines the role of different epigenetic mechanisms in the regulation and maintenance of mammalian genome and focuses on the role of dietary phytochemicals as epigenetic modifiers in cancer. Above all, the review focuses on summarizing the progress made thus far in cancer chemoprevention with dietary phytochemicals, the heightened interest and challenges in the future.

Keywords

cancer chemoprevention; dietary agents; epigenetics; DNA methylation; histone modification; microRNA; plant polyphenols

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CONFLICT OF INTEREST

The authors have no competing interest.

1.0 Introduction

The term '*Epigenetics'* was coined by British developmental biologist Conrad Waddington, derived from the combination of word 'epigenesis' and 'genetics' [1]. Epigenetics is defined as the branch of biology which studies the casual interactions between genes and their products, where '*Epi'* means above or over and 'genetics' reflects the involvement of genes and heredity. Today *epigenetics* may be defined as the study of chemical changes to the genome that are heritable and modulate gene expression or cellular phenotype through mechanisms involving how DNA is packaged and expressed without any alterations in the gene nucleotide sequence itself [1, 2]. Epigenetic mechanisms have been shown to be essential in regulating normal cellular functions and play important role during developmental stages. In mammals, DNA methylation is associated with several key processes such as genomic imprinting, X-chromosome inactivation and tissue-specific gene expression [3–6]. Histone methylation and acetylation patterns were demonstrated to be closely associated with cognitive functions such as long term memory formation and storage [7–9]. Epigenetic alterations have been implicated in several pathologies such as cancer, metabolic syndrome, Alzheimer's disease and other neurological disorders [10–13]. Unlike genetic changes in the genome such as mutation, epigenetic modifications are potentially reversible and can be modified by environmental, dietary and lifestyle factors. Epigenetic mechanisms have been implicated in physiological responses to intrinsic and extrinsic environmental stimuli such as nutrition, radiation, exposure to chemicals, toxins and hormones [14, 15]. The epigenetic diet, or the control of epigenetic modifiers through consumption of dietary phytochemicals, is of extreme interest. Several studies suggest that dietary phytochemicals are not only an essential source of nutrients but also important in the elimination of cancer as a life-threatening disease [14, 15]. In this review, we focused on the role of dietary phytochemicals as epigenetic modifiers. We discussed in detail different mechanisms of epigenetic modifications in mammals and present a comprehensive overview of the current state of knowledge on dietary bioactive compounds and their influence on various epigenetic mechanisms highlighting their role as potential anticancer agents.

2.0 Mechanisms of epigenetic modifications

Although a number of epigenetic mechanisms have now been identified, in mammals there are three major epigenetic mechanisms which are known to regulate gene expression. These include DNA methylation, alteration of chromatin structure by post-translational modification of histone or non-histone proteins, and small non-coding microRNAs (miRNAs) that modulate gene expression by either inhibiting translation or causing targeted degradation of specific mRNAs [15, 16].

2.1 DNA methylation

Methylation of cytosine residues within the dinucleotide sequence-CG is one of the most widely studied epigenetic modifications in mammals [17]. Forming an essential component of the cellular epigenetic machinery, DNA methylation in cooperation with histone modification regulates gene expression by modulating DNA packaging and chromatin architecture [18, 19]. DNA methylation is a chemical modification that involves the transfer

of a methyl (CH_3) moiety from the donor *S*-adenosyl methionine (SAM) to the 5′ position of cytosine residue that precedes guanine in the CG dinucleotide sequence, forming 5-methyl cytosine and *S*-adenosyl-L-homocysteine (SAH) [17, 20–22]. The mammalian genome has been reported to harbor 3×10^7 methylated cytosine residues mostly within CG dinucleotide sequences [21]. Although CG sequences are unevenly distributed throughout the human genome, they are frequently enriched in gene promoters (often referred as *CpG islands*) and large repetitive sequences such as LINE and ALU retrotransposon elements [23]. In mammals, most CpG islands are methylated on cytosine residues by a group of enzymes known as DNA methyltransferases (DNMTs), whereas CpG islands within gene promoters tend to be protected from methylation [17, 23]. In cancer, increased DNA methylation has been observed in the CpG islands in the promoter region of some genes that function as a 'switch' resulting in gene silencing. Although no mutation or deficiency in any DNMTs has been identified as causally linked to tumor development, most likely because of their critical role during embryogenesis. So far, there are three major DNA methyltransferases (DNMT1, DNMT3a and DNMT3b) identified in mammals. DNMT1 enzyme has been demonstrated to have a 5–30 fold more preference for hemi-methylated substrates and therefore popularly designated as maintenance methyltransferase. It preserves the existing methylation patterns in the daughter DNA strands by adding methyl groups to hemi-methylated CpG sequences following replication. DNMT1 has been demonstrated to be involved in *de novo* methylation activity in embryo lysates and its sequence specificity was shown to be confined to 5′-CpG-3′ dinucleotide sequence with little dependence on sequence context or density [24]. DNMT3a and DNMT3b enzymes are essential for global *de novo* methylation as they preferentially target unmethylated CpG sequences [25]. Although DNMT3L, the fourth family member, lacks intrinsic DNMT activity by itself, it co-localizes with DNMT3a and DNMT3b to establish genomic imprints in maternal germ line and facilitate methylation of retroposons [26–28]. DNMT2, another enigmatic member of DNMT family, was found to lack any biochemically detectable DNMT activity. Evidences from phenotypic analyses of mice with mutant DNMT genes have provided useful mechanistic insights into the role and establishment of DNA methylation patterns during development [15, 21].

Hypermethylation of CpG islands is usually associated with gene silencing. There are multiple routes through which DNA methylation can suppress transcription. A general mechanism is to exclude binding of proteins that modulate transcription through their DNA binding domains [29]. This mechanism has been demonstrated to be essential for imprinting of *Igf2* gene [30]. CpG methylation has also been shown to block the binding of several other transcription factors, however their biological consequences remain unknown [31]. Another mechanism for DNA methylation mediated gene repression involve binding of specialized DNA binding proteins to the methylated CpG stretches, which form repressor complexes with histone deacetylases (HDACs) and cause chromatin compaction [32–34]. In mammals six methyl-CpG-binding proteins have been characterized till date, which include MeCp2, MBD1-4 and Kaiso. Studies demonstrate that all of them (except mammalian MBD3) possess a domain that specifically targets them to methylated CpG regions *in vitro* and *in vivo* [33, 35, 36]. Several detailed reviews are available discussing about DNA

methylation, their role in cancer and development as biomarkers, which is currently beyond the scope of this review [37–39].

2.2 Histone Modifications

In addition to DNA methylation, post-translational modification of N-terminal histone tails play a significant role in epigenetic regulation of gene expression [40, 41]. A typical nucleosome unit consists of ~146 bp of DNA wrapped around an octamer of histones (H2A, H2B, H3 and H4) represent the fundamental building unit of eukaryotic chromatin. A diverse array of covalent chemical modification of less structured, protruding N-terminal tails of core histones by methylation, acetylation, ubiquitination, phosphorylation, sumoylation and ADP-ribosylation dictate the dynamics of chromatin state [42]. Euchromatin is lightly packed form of chromatin where DNA is accessible for transcription whereas heterochromatin represents tightly packed chromatin state inaccessible to cellular transcriptional machinery. Most of the chemical modifications occur at lysine (K), arginine (R) and serine (S) residues within the histone tails. These distinct histone modifications on one or more histone tails (often referred to as ‘histone code’) which may act sequentially or in combination are recognized by other proteins that signal further downstream events.

A number of enzymes have been implicated in catalyzing (addition or removal) various histone modifications. Examples include histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases (HMTs), histone demethylases (HDMs), histone kinases etc. In brief, HATs catalyze the addition of acetyl group on the ε-amino group of lysine residues in the N-terminal tail of histones, which neutralize the positive charge, relax the chromatin and facilitate binding of transcriptional machinery to the DNA [43]. Till date, 25 HATs have been characterized which are divided into four families. Examples include GNAT (*hGCN5, PCAF*), MYST (*MYST, Tip60*), p300/CBP (*p300/CBP*, SRC (*SRC-1*) and TAFII250 families (TAFII250) [44, 45]. In contrast, HDACs catalyze the removal of acetyl groups from K residues resulting in the compaction of chromatin configuration repressing gene transcription [45]. HDACs are classified into four groups. HDAC-1, -2, -3 and -8 are members of class I HDAC family while HDAC-4, -5, -6, -7, -9 and -10 belong to class II HDAC family. HDAC-11 belongs to class IV HDAC group. Sirtuins which require NAD^+ as cofactor for their activity and are structurally unrelated to other HDAC classes, constitute class III HDAC family [46, 47]. HMTs catalyze the addition of methyl groups to K or R residues while HDMs act to remove them [45–47]. Examples of histone lysine methyltransferase include EZH2 (enhancer of zeste homolog 2) and that of histone lysine demethylase include LSD1 (lysine specific demethylase 1) [48, 49]. Depending on the site of lysine methylation (K4, K9, K27 in histone H3) and methylation status (mono, di or tri methylation), histone methylation may have activating or repressive effect on gene expression [41, 49]. H3K4, H3K36 and H3K79 methylation have activating effects on gene transcription whereas methylation of H3K9, H3K27 and H4K20 is generally associated with gene silencing or transcriptional repression [41, 47, 50]. Several excellent reviews are available on each group of histone modifying enzymes, their mechanism of action and various histone modifications for biomarker and assay development, which is beyond the scope of this review [51, 52].

2.3 Non-coding RNAs

Recent evidences indicate that non-coding RNA (ncRNA) transcripts play fundamental role in epigenetic regulation of gene expression and have been implicated in various epigenetic mechanisms such as transposon silencing, X-chromosome inactivation, DNA imprinting, and paramutation [53–55]. In humans, ncRNAs include microRNA (miRNA), small interfering RNA (siRNA), piwi-interacting RNA (piRNA) which accounts for majority of transcripts, representing approximately 98% of all human transcriptional output [56, 57]. Based on the size, ncRNA can be classified into small ncRNA which are generally less than 200 nucleotides in length and long ncRNA (lncRNA) transcripts that are more than 200 nucleotides in length. Small ncRNAs particularly miRNAs regulate key epigenetic mechanisms. MiRNAs are known to regulate various components of cellular epigenetic machinery particularly polycomb complexes and thus affect multiple downstream effects [53, 58–60]. One such example include miR-214 which downregulates EZH2 expression by targeting its 3′-UTR region and accelerates skeletal muscle differentiation and transcription of developmental regulators in embryonic stem cells [61]. There are other miRNAs which have been implicated in the repression of Bmi1, a component of PRC1 complex [62–64]. DNA methylation has also been shown to be modulated by miRNAs. DNMT1 and 3 have been reported to be targeted by the miR-29 family in lung cancer and leukemia cells [65, 66]. In summary, recent evidences suggest that ncRNAs have emerged has key regulators of epigenetic mechanisms and also, that the modulation of these RNA transcripts by the same epigenetic processes may lead to major consequences. Several excellent publications are available on each group of ncRNAs, their mechanism of action affecting gene regulation, which is beyond the scope of this review [67, 68].

3.0 Epigenetic mechanisms regulated by dietary phytochemicals

Unlike genetic modifications, epigenetic states of genes are reversible and can be altered by certain intrinsic and extrinsic factors. This characteristic of epigenetic mechanism may lead to the development of abnormal phenotype as well as regulate physiological response to some environmental stimuli, diet or therapeutic intervention [15]. In past two decades, accumulated evidences show that dietary phytochemicals present in abundance in fruits, vegetables and beverages which were earlier known only for their antioxidant or chemopreventive effects are also potent epigenetic regulators, which could target or revert abnormal epigenetic modifications in various human pathologies including cancer [20, 69–77]. Here we describe some common dietary phytochemicals, their structure and molecular weight, which are potent epigenetic modifiers (Table 1). These dietary phytochemicals have shown potential as DNMT inhibitors, histone modifiers and vary miRNA level altering gene expression and restoring the expression of various tumor suppressor genes which are summarized in Tables 2–4. We also discuss the progress made on some potential dietary phytochemicals in clinical trials (Table 5). Some popular dietary phytochemicals are discussed in detail below.

3.1 Apigenin

Apigenin is a dietary plant flavonoid, chemically known as 4′,5,7,-trihydroxyflavone, present in common fruits and vegetables such as parsley, onions, oranges, tea, chamomile

and wheat sprouts [78]. Previous studies have confirmed that apigenin possess antioxidant, anticancer, anti-inflammatory and anti-mutagenic properties [79–84]. However, the effect of apigenin on epigenetic-related enzymes and their mechanisms was not recognized until recently. Apigenin treatment (20 and 50 μM) was shown to cause a marked decrease in DNMT activity *in vitro* [85]. Studies from our laboratory demonstrated that apigenin-mediated growth arrest and apoptosis in human prostate cancer PC-3 and 22Rv1 cells was due to inhibition of class I HDACs [86]. In vivo studies using PC-3 xenografts in athymic nude mice further confirmed that oral intake of 20 and 50 μg/day apigenin over an 8-week period reduces tumor burden, HDAC activity and HDAC-1 and HDAC-3 protein levels. HDAC-1 and HDAC-3 mRNA and protein levels were found to be significantly decreased in these cells after 20–40 μM apigenin treatment with consequential increase in global histone H3 and H4 acetylation. A corresponding elevation in p21/waf1 and Bax levels was observed in both *in vitro* and *in vivo* studies, which resulted in induction of apoptosis and cell cycle arrest in tumor cells. In a recent study by Paredes-Gonzalez et al. [87], apigenin was shown to reactivate Nrf2 gene which encodes a key transcription factor known to regulate anti-oxidative defense system and skin homeostasis, in mouse skin epidermal JB6 P+ cells via epigenetic mechanisms. Hypermethylation of 15 CpG sites in Nrf2 promoter was demonstrated to be reversed by apigenin treatment in a dose-dependent manner. Apigenin exposure also resulted in decrease expression of DNMT1, DNMT3A, DNMT3B and HDAC 1–8 levels. Furthermore, nuclear localization of Nrf2 was enhanced along with increase expression of Nrf2 and its target gene NQO1 after apigenin treatment.

3.2 Curcumin

Curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is the major active component of popular South Asian spice turmeric (*Curcuma longa*), belonging to *Zingiberaceae* (ginger) family. The majority of health-benefits associated with turmeric intake has been attributed to curcumin which include anti-microbial, antioxidant, anti-inflammatory, anti-allergic and anti-carcinogenic effects [88–91]. At the molecular level, curcumin has been shown to modulate multiple intracellular pathways associated with proliferation, survival, invasion, apoptosis and inflammation [92]. In the context of epigenetic pathways, several studies have reported curcumin to be a potent modulator of DNMTs, histone modifying enzymes including HDACs and HATs and miRNAs [93]. *In silico* molecular docking studies of curcumin with DNMT1 revealed its ability to block and/or inhibit the catalytic thiol group of C1226 binding site in the enzyme resulting in decreased DNMT activity [93]. This study was further validated by *in vitro* experimental studies which showed curcumin to be a potent DNA hypo-methylating agent [94]. Curcumin was reported to be an effective HDAC inhibitor in HeLa nuclear extracts with an IC_{50} value of 115 μM. Docking studies performed with curcumin binding to HDAC-8 revealed it to be more potent inhibitor of HDAC than known pharmacological inhibitors such as sodium butyrate and valproic acid [95]. Another study reported that curcumin treatment to B-NHL Raji cells reduces HDAC-1, HDAC-3 and HDAC-8 protein expression in a dose-dependent manner and increases H4 acetylation in these cells [96]. Consistence with earlier findings, studies by Chen et al. [97] reported significant reduction in p300/CREB binding protein (CBP), HDAC-1 and HDAC-3 levels after exposure of Raji cells to curcumin. This decrease in HDACs and CBP levels were implicated in curcumin-mediated repression of NF-κB and

Notch1, which resulted in decrease proliferation of Raji cells. Studies revealed curcumin as a specific inhibitor of p300/CBP HAT, which emerged as a novel target for cancer treatment [98–100]. Curcumin treatment caused proteasomal degradation of p300 and other closely related CBP proteins with no effect on HATs such as GCN5 and PCAF [100]. In addition, curcumin-mediated inhibition of p300/CBP was found to block HDAC inhibitor MS-275 induced histone hyper-acetylation in prostate cancer PC3-M cells and peripheral blood lymphocytes. Curcumin has been shown to epigenetically up-regulate *DLEC1* and reduce CpG methylation in HT29 cells, lowering protein expression of DNMTs and HDACs attenuating clonogenicity of human colorectal adenocarcinoma HT29 cells [101]. In another study, curcumin has been shown to act as dual agent in causing apoptosis and reversal of promoter methylation of *p15* gene in ALL leukemia cells [102].

The chemotherapeutic and chemopreventive effects of curcumin has also been closely linked to its ability to modulate miRNAs in cancer cells. A microarray based study of the effect of curcumin (10 μM) on the miRNA profile in pancreatic cancer PxBC-3 cells showed significant changes in the expression of 29 miRNAs (11 upregulated and 18 downregulated) after 72 h treatment [103]. Further studies confirmed that miR-22, which has tumor suppressive function, was upregulated after exposure to curcumin and its downstream target genes *SP1* and *ESR1* were suppressed in these cells. Ali et al. [104] demonstrated that treatment of pancreatic cancer cells with curcumin and its analogue CDF could induce gemcitabine sensitivity via induction of miR-200 and inactivation of miR-21 expression. These studies underline the importance of curcumin-mediated modulation of miRNAs as an important mechanism for its biological effects. Curcumin has been reported to reduce DNMT3B activation leading to hypomethylation of *RARβ* resulting in upregulation of its expression [105]. Dendrasomal curcumin has been shown to induce DNA hypomethylation in part via up-regulation of epi-miRs, leading to the re-expression of silenced tumor suppressor genes including *MEG3*, and suppress oncogenes including HOTAIR, targeting histone modifying complexes in hepatocellular carcinoma HCC cells [106].

3.3 Green tea polyphenols and epigallocatechin-3-gallate (EGCG)

EGCG, the major constituent present in green tea, is widely known for its health-related benefits. Other major constituents present in green tea are epicatechin-3-gallate, epigallocatechin, and epicatechin. These polyphenols have been shown to possess multifaceted effect on various cellular targets at the molecular level including epigenetic pathways or enzymes [107, 108]. Several studies have demonstrated that EGCG is a potent demethylating agent which inhibits enzymes involved in DNA methylation and is an effective histone modifying agent [109–116]. It is well known that CpG island hypermethylation at the promoter region leads to epigenetic repression of several critical tumor suppressor genes during tumorigenesis. Fang et al. [109] reported that EGCG acts as a competitive inhibitor of *DNMT* (Ki=6.89 μM), which binds to the catalytic pocket and inhibit DNMT activity in a dose-dependent manner. Furthermore, EGCG treatment (5–50 μM for 12–144 h) was found to effectively reactivate methylation-silenced genes *viz. p16* (*INK4a*), retinoic acid receptor beta (*RARβ*), O(6)-methylguanine methyltransferase (*MGMT*), and human mutL homologue 1 (*hMLH1*), in human esophageal cancer KYSE 510 cells. EGCG was also reported to inhibit HDACs and increase permissive or active histone

modifications such as histone acetylation at the target gene promoters. Studies from our laboratory by Pandey et al. [110] showed that exposure of prostate cancer cells to green tea polyphenols (GTP) caused re-expression of epigenetically silenced *glutathione-S transferase pi* (*GSTP1*) gene which correlated with the promoter demethylation due to DNMT1 inhibition and histone modification at the promoter region. However, GTP treatment did not show any global hypomethylation effect which could result in genomic instability assessed by the methylation status of LINE-1 promoter remained unaffected. GTP treatment decreased mRNA and protein levels of MBD1, MBD4, MeCP2, HDAC 1–3 whereas acetylated histone H3 (LysH9/18) and H4 were found to be elevated. Another study from our group by Thakur et al. [111], demonstrated that GTP treatment caused cell cycle arrest and apoptosis by inducing proteasomal degradation of class I HDACs in human prostate cancer cells. Studies by Li et al. [112] demonstrated that EGCG in combination with class I HDAC inhibitor, trichostatin A (TSA) could synergistically reactivate ERα expression in ERα negative MDA-MB-231 breast cancer cells by modulating histone methylation and acetylation pattern at the gene promoter. In addition, they also reported that treatment with EGCG and/or TSA contributes to transcriptional activation of ERα by causing a decreased binding of transcription repressor complex, Rb/p130-E2F4/5-HDAC1-SUV39H1-DNMT1 to the regulatory region of the gene. Nandkumar et al. [113] demonstrated that EGCG reactivates silenced tumor suppressor genes Cip1/p21 and p16INK4a by reduction in DNA methylation and increase in histone acetylation in human skin cancer cells.

EGCG has been reported to modulate polycomb proteins such as Bmi-1 and EZH2 [114, 115]. EGCG alone or in combination with 3-Deazaneplanocin A (DZNep), an EZH2 inhibitor was shown to decrease polycomb group proteins (PcG) proteins including EZH2, EED, SUZ12, MEL18 and Bmi-1 via a mechanism involving proteasome associated degradation. The reduction in PcG proteins correlated with a decrease in repressive chromatin marks *viz*. H3K27me3 and H2AK119ub and HDAC-1 whereas accumulation of acetylated H3 levels was found to be elevated in skin cancer SCC-13 and human epidermoid carcinoma A431 cells [114, 115]. In a recent study form our group, Deb et al. [116] reported that EGCG and/or GTP treatment to breast cancer cells induced expression of epigenetically repressed *TIMP-3* gene, which is mediated by modulating epigenetic mechanisms involving EZH2 and class I HDACs independent of the promoter DNA methylation. After EGCG or GTP treatment, protein levels of class I HDACs and EZH2 were significantly reduced. Interestingly, transcriptional activation of TIMP-3 was associated with decreased EZH2 localization and H3K27me3 at the promoter with a concomitant elevation in H3K9/18 acetylation levels. Time-dependent exposure to EGCG resulted in reactivation of known tumor-suppressor genes in HeLa cells due to marked changes in the methylation of the promoter regions of these genes [117]. In cystic and adenoid cystic carcinoma SACC83 cells, EGCG significantly enhanced the protein and mRNA expression levels of RECK, and markedly reduced the invasive ability of these cells [118]. Jha et al. [119] demonstrated the dual inhibitory effect of EGCG in oral squamous carcinoma cells. In this study, EGCG has been reported to efficaciously reduce DNA methylation catalyzed by SssI methyltransferase and human DNMT1 and inhibited DNMT activity by increasing the level of SAH in the methylation reaction catalyzed by catechol-O-methyl transferase (COMT). Additionally, EGCG also interacted directly with the catalytic site of human DNMT1. Chen et al. [120]

performed a genome wide methylation and mRNA expression screen in oral squamous carcinoma OSCC cells after EGCG treatment that revealed a total of 761 differentially methylated gene loci. Comparison of gene expression profiling revealed 184 transcripts with a significant difference and fold change. Gene ontology analysis of differentially methylated loci and functional annotation of differentially expressed genes indicated that the main pathways involved were metabolic, mitogen activated protein kinase (MAPK), Wnt signaling, and cell cycle pathways suggesting EGCG can affect the methylation status and gene expression.

3.4 Genistein and soy isoflavones

Genistein is a phyto-estrogen belonging to isoflavone group. Isoflavones such as genistein, biochanin A and daidzein occur naturally in plant sources such as soybeans, fava beans, lupine, kudzu, psoralea etc. [121, 122]. Till date, numerous epidemiological and experimental studies have demonstrated the chemopreventive effects of genistein and other isoflavones on various cancer types including breast and prostate cancer [123]. In recent years, the role of genistein and other soy isoflavones as epigenetic modulators regulating gene expression has been widely reported by several studies. Genistein has been shown to be a more potent DNMT inhibitor as compared to biochanin A or daidzein. Fang et al. [124] reported that genistein (2–20 μM) could reactivate methylation-silenced genes such as retinoic acid receptor beta (*RARβ*), *p16INK4a*, and *MGMT* in esophageal squamous carcinoma cells KYSE 510 and prostate cancer LNCaP and PC3 cells. Reactivation of such genes by direct inhibition of DNMT may be one of the factors contributing to the chemopreventive effects of soy isoflavones. In another study, Li et al. [125] demonstrated that genistein treatment in breast MCF10AT benign cells and MCF-7 cancer cells depletes telomerase (hTERT) activity through epigenetic modification which involves genistein-mediated decrease in DNMT1, DNMT3a and DNMT3b levels. Site-specific hypomethylation in hTERT promoter was found to increase the binding of E2F-1 transcription factor. Furthermore, genistein was shown to repress hTERT promoter by chromatin remodeling which involved increase in trimethyl-H3K9 enrichment with a concomitant decrease in dimetyl-H3K4 chromatin marks. Studies by King-Batoon et al. [126] showed that low, non-toxic dose of genistein (3.125 μM, re-supplemented every 48 h for 1 week) could partially demethylate *GSTP1*, a tumor suppressor gene, in MCF-7, MDA-MB-468 and MCF10A breast cells. Similar *in vitro* studies on other cancer types provide evidence that genistein is a potent demethylating as well as histone modifying agent, which could reverse the silenced state of critical tumor suppressor genes [127–129]. Genistein, daidzein, daidzein metabolite equol and AglyMax have been reported to induce ERα-mediated histone acetylation via modulation of HAT activity [130]. Majid et al. [131] demonstrated that genistein-mediated epigenetic induction of *p21waf1/Cip1* and *p16INK4a* tumor suppressor genes in human prostate cancer cells involve chromatin modification via upregulation of HATs expression. In another study, Basak et al. [132] demonstrated that androgen receptor (AR) down-regulation in prostate cancer LNCaP cells by genistein was attributed to the inhibition of HDAC6-Hsp90 co-chaperone function, which is required for AR protein stabilization. Genistein and daidzein treatment in prostate cancer cells caused alterations in the methylation profiles of 58 genes [133]. Both these agents caused modifications in the methylation frequencies of MAD1-like 1 (*MAD1L1*), tumor necrosis

factor receptor-associated factor 7 (*TRAF7*), lysine (K)-specific demethylase 4B (*KDM4B*), and human telomerase reverse transcriptase (*hTERT*) genes. Furthermore, genistein treatment in prostate cancer cells increased ER-β levels reducing its promoter methylation that is required in preventing cell proliferation [134]. However, *in vivo* clinical studies were inconclusive and did not fall in line with the studies performed in cell line models. In a randomized trial study involving thirty four healthy pre-menopausal women to investigate the estrogenic and methylation effect of soy isoflavones (40 mg or 140 mg daily) through one menstrual cycle, Qin et al. [135] reported that considering all subjects or by dose there were no significant changes for any of the cancer related genes (*p16INK4a, RASSF1A, RARβ2, ER, and CCND2*). In fact, *RARβ2* methylation was shown to increase post-treatment at circulating genistein levels greater than 600 ng/ml unlike the effect observed for genistein levels below 600 ng/ml. Similarly, *CCND2* methylation was found to increase in subjects with post-treatment genistein levels above 200 ng/ml as opposed to the effects observed below this genistein levels. Changes in the methylation of other genes *p16INK4a, RASSF1A and ER* did not correlate with post-treatment genistein levels.

Genistein and other soy isoflavones have shown to module miRNAs as well. Parker et al. [136] performed miRNA profiling of genistein treated and untreated ovarian cancer UL-3A and UL-3B cells and found 53 differentially expressed miRNAs. Upregulation of miR-200 and let-7 by isoflavones was shown to down-regulate ZEB1, slug and vimentin and therefore cause reversal of epithelial to mesenchymal transition in gemcitabine resistant pancreatic cancer cells [137]. In human uveal melanoma cells, genistein treatment demonstrated significant growth inhibition by targeting miR-27a and its target *ZBTB10* [138]. In colorectal cancer cells, genistein has been shown to reduce miR-95, Akt and SGK1 to inhibit cell growth while in breast cancer cells it increased the levels of miR-23b to attenuate proliferation [139, 140].

3.5 Indole-3-carbinol and diindolylmethane

Indole-3-carbinol (I3C) is a hydrolysis product derived from a glucosinolate catalyzed by the plant enzyme myrosinase, which is further metabolized under the acidic conditions in the stomach to form dimer 3,3′-diindolylmethane (DIM) [141–143]. These phytochemicals are present in cruciferous vegetables particularly *Brassica* genus which include broccoli, cabbage, cauliflower, brussel sprouts, mustard, radish etc. [144]. Both these phytochemicals have been shown to exert anticancer effects by down-regulating multiple cellular targets and inducing cell cycle arrest and apoptosis in various cancer types [144, 145]. A recent study by Li et al. [146] demonstrated that DIM selectively induce proteasomal degradation of class I HDACs (HDAC-1, -2, -3 and -8) with no effect on class II HDACs, both in human colon cancer cells *in vitro* and *in vivo* in tumor xenografts. Furthermore, depletion of class I HDACs was shown to relieve transcription repression of cyclin-dependent kinase inhibitors *p21/waf1* and *p27/Kip2*, which ultimately resulted in G2 arrest and DNA damage triggered apoptosis. In another study, Beaver et al. [147] examined the effects of I3C and DIM on prostate cancer LNCaP and PC-3 cells, which differ in their androgen receptor status. DIM was shown to inhibit HDAC activity in both cell lines; however I3C demonstrated modest inhibition of HDAC activity in androgen-responsive LNCaP cells with no significant effect on androgen-refractory PC-3 cells. A significant decrease in HDAC-2 protein levels was

reported in both cell lines after DIM treatment but the levels of HDAC-1, HDAC-3, HDAC-4, HDAC-6, and HDAC-8 remained unaltered. Interestingly, a recent study by Busbee et al. [148] reported that I3C and DIM may decrease activation, proliferation and cytokine production by staphylococcal enterotoxin B-induced T cells *in vitro* and *in vivo* by acting as class I HDAC inhibitors.

In a study to examine the effect of DIM on miRNA expression profile between gemcitabine-sensitive and gemcitabine-resistant pancreatic cancer cells, Li et al. [149] reported that DIM treatment caused significant upregulation of members of miR-200 and let-7 families. Furthermore, re-expression of miR-200 in gemcitabine-resistant cells was found to be associated with a corresponding downregulation of mesenchymal markers ZEB1, slug and vimentin and upregulation of epithelial marker E-cadherin, which lead to the reversal of EMT phenotype to epithelial morphology. In another study, DIM treatment was demonstrated to increase the expression of miR-146a which correlated with reduced expression of EGFR, MTA-2, IRAK-1, and NF-κB, ultimately resulting in the inhibition of pancreatic cancer cell invasion [150]. In human breast cancer MCF-7 (estrogen receptor positive) and MDA-MB-468 (p53 mutant) cells, DIM treatment was demonstrated to augment G2/M cell cycle arrest by down-regulating the expression of Cdk-2, Cdk-4 and Cdc25A [151]. In addition DIM treatment was shown to cause upregulation of miR-21 which negatively regulates Cdc25A resulting in decreased breast cancer cell proliferation. Similar studies were reported with I3C which targets the PTEN/AKT signaling pathway and downregulates miR-21. Down-regulation of miR-21 was shown to further reduce resistance of HCC cells to I3C through inhibition of PTEN/AKT pathway *in vivo*.

3.6 Lycopene

Lycopene is the bright red carotene pigment belonging to tetra terpenoids and a phytochemical which occur naturally in tomatoes, carrot, watermelon, papaya, cherries etc. It is a potent anti-oxidant and has been shown to modulate multiple genes involved in DNA repair, cell cycle control and apoptosis in breast cancer cells [152, 153]. Studies by King-Batoon et al. [126] reported the effects of lycopene on *GSTP1* gene in breast cancer cells. Lycopene (2 μM for 1 week) was shown to induce GSTP1 expression and demethylate GSTP1 promoter in MDA-MB-468 cell line but not in MCF-7 breast cancer cells. The expression of other genes such as *RARβ2* and *HIN1* remained unaltered by lycopene treatment in MCF-7 and MDA-MB-468 breast cancer cells. Although this study has shown that lycopene may be DNA methylating agent but further studies are needed to decipher the lycopene-mediated effects on epigenetic mechanisms. The protective effect of lycopene on the prostate is different between androgen-responsive and androgen-refractory derived prostate cancer cells. Fu et al. [154] demonstrated that lycopene treatment significantly decreased methylation levels of GSTP1 promoter and increased the mRNA and protein levels of GSTP1 in an androgen-refractory PC-3 cells. It also caused decrease in DNMT3A expression in PC-3 cells while no such change were observed in LNCaP cells.

3.7 Organosulfur compounds

Vegetables such as onion, garlic, shallots etc. belonging to allium family possess various water and fat soluble organosulfur compounds (OSCs) which have been widely implicated

for numerous health-related benefits including cancer prevention, improved immunity, cardiovascular health and anti–microbial activity [155, 156]. Conversion of alliin to allicin and other alkyl alkane-thiosulfinates by the enzyme alliinase generate OSCs, which further decompose to more stable sulfur compounds such as diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DATS). S-allylmercaptocysteine (SAMC) is the active metabolite derived from DADS, both of which are finally converted to allyl mercaptan (AM) and other metabolites [157]. Accumulated evidences suggest that in human cancer cells these OSCs increase histone (H3/H4) acetylation, highlighting HDACs as their potential targets [157–159]. In colon cancer Caco-2 and HT-29 cells, DADS was reported to inhibit cell proliferation and cause G2 cell cycle arrest by inhibiting HDAC activity, inducing histone hyperacetylation as well as p21 (Waf1/cip1) expression [160]. Furthermore, treatment of human colon cancer cells with AM caused accumulation of acetylated histones in cellular chromatin and facilitated binding of transcription factor SP3, followed by recruitment of p53 at the p21/waf1 promoter. Similarly, a study by Nian et al. [161] where several garlic derived OSCs were tested or screened *in vitro* for their ability to inhibit HDACs. They reported that AM was the most potent HDAC inhibitor. Further experiments which include molecular modeling, structure-activity and enzyme kinetic studies confirmed competitive inhibition of HDAC-8 by AM (Ki=24 μM).

3.8 Phenethyl isothiocyanate (PEITC)

Isothiocyanates are metabolites of glucosinolates which occur naturally in cruciferous vegetables [19]. PEITC is a metabolite of gluconasturtin obtained from water cress, which has shown significant beneficial health-related effects particularly in cancer chemoprevention [162]. Like other natural phytochemicals, PEITC have been demonstrated to regulate epigenetic mechanisms by modulating DNA methylation and histone modifications. Studies by Wang et al. [163] reported dual action of PEITC treatment on DNA methylation as well as histone modifications in epigenetic re-activation of *GSTP1* gene in prostate cancer cells. Exposure of prostate cancer LNCaP cells to PEITC inhibited HDAC activity and concurrently demethylate the promoter to restore the GSTP1 levels to that found in normal prostate cells. In another study, exposure of mouse erythroleukemic cells to allyl isothiocyanates was found to increase acetylation of histones, with no significant effect on histone deacetylation [158, 159].

3.9 Quercetin

Quercetin is a dietary flavonoid abundantly present in citrus fruits, onion and buckwheat. Studies have shown that this bio-flavonoid is a potent free radical scavenger or anti-oxidant as well as a chemopreventive agent with pro-apoptotic and growth inhibitory effects on cancer cells [164]. Tan et al. [165] investigated the *in vitro* effects of quercetin on human colon cancer RKO cells and showed that the hypermethylation status of *p16INK4a* gene could be completely reversed after quercetin treatment in a dose-dependent manner. In another study, quercetin was shown to downregulate tumor necrosis factor (TNF)-induced interferon-gamma-inducible protein 10 (IP-10) and macrophage inflammatory protein 2 (*MIP-2*) gene expression in murine intestinal epithelial cells. At the molecular level, quercetin treatment was found to cease recruitment of cAMP response element binding protein (CBP)/p300 and histone H3 phosphorylation/acetylation at the gene promoters as

well as inhibition of histone acetyltransferase activity [166]. Studies by Lee et al. [167] demonstrate that in human leukemic HL-60 cells, quercetin treatment induced Fas-L related apoptosis and activation of the ERK (extracellular signal–regulated kinase) and JNK (Jun N-terminus kinase) signaling pathways. Quercetin treatment was found to increase histone H3 acetylation which in turn caused increased expression of Fas-L. Furthermore, quercetin treatment resulted in the activation of HAT and inhibition of HDAC; however HAT activation was found to be only associated with ERK and JNK pathways. Priyadarsini et al. [168] reported a positive correlation between HDAC1 and DNMT1 inhibition by quercetin and its anti-tumor properties such as pro-apoptosis, anti-angiogenesis and anti-invasiveness. In a recent study, Ravichandran et al. [169] proposed a refined pharmacophore model for quercetin binding site of SIRT6 protein. This study was in continuation from a previous study reporting quercetin to be a potent SIRT6 inhibitor and identified a preliminary pharmacophore for quercetin binding (consisting of three hydrogen bond donor and one hydrogen bond acceptor) on the SIRT6 histone deacetylase [170]. Quercetin has been demonstrated to induce histone acetylation (H3K56ac) in cultured cells inhibiting SIRT6 that has a critical role in several types of cancer [171].

Quercetin has shown to module miRNAs in various human cancers as well. Using gastric cancer cells, Du et al. [172] demonstrated that quercetin in the presence of miR-143 caused autophagy inhibition via targeting GABARAPL1. In another study, Sonoki et al. [173] demonstrated that quercetin decreased claudin-2 expression and instability of mRNA in lung adenocarcinoma cells mediated by upregulation of miR-16 expression. Treatment of hepatocellular carcinoma cells with quercetin has been shown to involve miR-34a to enhance apoptosis signal through a p53/miR-34a/SIRT1 signal feedback loop [174]. In another study, modulation of miR-217-KRAS axis in osteosarcoma by quercetin enhanced cisplatin sensitivity, regulating the resistance of cancer to chemotherapeutic drugs [175]. In androgen-refractory prostate cancer cells quercetin treatment caused apoptosis, inhibited invasion and migration capabilities and reduced the expression of numerous prostate tumor associated miRNAs, including miR-21. Quercetin increased the expression of tumor suppressor programmed cell death protein 4, that negatively regulate miR-21 in these cells [176].

3.10 Resveratrol

Resveratrol (trans-3,4′,5-trihydroxystilbene), a plant derived polyphenolic compound present in grapes, wine and root extracts of the weed *Polygonum cuspidatum*, has been identified as a potent anti-aging, anti-inflammatory and chemopreventive agent affecting various molecular targets [177, 178]. Focusing on epigenetic pathways related cellular targets, SIRT1 and acetyl transferase p300 were reported be the activated by resveratrol [179–181]. Resveratrol was identified as a potent dietary activator of SIRT1, which lowers the Km (Michaelis constant) for both acetylated substrate and NAD+. It was reported to stimulate SIRT1-dependent p53 deacetylation which ultimately contributes to increased cell survival [180, 181]. In a study by Wood et al. [182], resveratrol was shown to activate sirtuins from metazoans - *Caenorhabditis elegans* and *Drosophila melanogaster* and delay aging without any effect on fecundity. The anti-tumor effect of resveratrol was reported to be mediated partly by SIRT1 [183]. Studies by Wang et al. [184] using SIRT1 mutant mice

demonstrated that disruption of SIRT1 function p53 null background causes tumor formation and resveratrol mediated activation of SIRT1 reduced tumorigenesis. In addition, resveratrol was shown to have a negative effect on *Survivin* gene expression through histone deacetylation at the gene promoter and display a more profound inhibitory effect on BRCA-1 mutant cells both *in vitro* and *in vivo*. Using prostate cancer cells, Kai et al. [185] demonstrated that resveratrol was able to cause downregulation of *MTA1* (metastasis associated protein), destabilize the NuRD (nucleosome remodeling deacetylase) complex and thus allowing p53 acetylation. Furthermore, activation of p53 was shown to induce pro-apoptotic pathways causing apoptosis in prostate cancer cells. In triple negative breast cancer cells, combination of resveratrol and pterostilbene administered at close to physiologically relevant doses caused synergistic (CI <1) growth inhibition by downregulating SIRT1. This combination also decreased the expression of γ-H2AX and telomerase expression affecting DNA damage and repair [186]. Resveratrol treatment of human bladder cancer EJ cells was found to lead to remarkable S-phase arrest and apoptotic cell death accompanied by loss of phosphorylation of STAT-3, leading to downregulation of the STAT-3 pathway as well as decreased nuclear translocation of SIRT1 and p53 [187]. Resveratrol has also shown to have a moderate inhibitory effect on DNMTs. Resveratrol treatment led to decreased DNMT1 and DNMT3b expression *in vitro*. In a rodent model of estrogen dependent mammary carcinoma, resveratrol treatment decreased DNMT3b expression in tumor samples but not in the normal tissues [188]. In another study, the chemopreventive effects of resveratrol were demonstrated *in vivo* by pre-exposing aromatic hydrocarbon receptor (AhR) agonist-treated pregnant Sprague-Dawley rats with resveratrol, an AhR-antagonist, which led to lesser CpG methylation of the *BRCA-1* gene [189].

Studies have demonstrated resveratrol induces apoptosis in a time-dependent and dose-dependent manner through increased expression level of miR-16-1 and miR-15a in leukemia cells [190]. In prostate cancer study with stilbenes has demonstrated miRNA-mediated (miR-17-5p and miR-106a-5p) therapeutic strategy, and proposed circulating miRNAs as predictive biomarkers for clinical development [191].

3.11 Sulforaphane

Sulforaphane (SFN) is an isothiocyanate abundantly present in broccoli, water crass, broccoli sprouts, cabbage and kale. SFN has been shown to modulate various physiological processes and affect various cellular pathways consistent with its chemopreventive effects which include induction of cell cycle arrest, apoptosis and xenobiotic metabolism [192, 193]. Microarray based transcriptome analysis of human colon Caco-2 cells treated with SFN at physiological concentrations showed downregulation of *DNMT1* gene as well as other genes known to be associated with carcinogenesis [194]. Studies by Meeran et al. [195] demonstrated that in MCF-7 and MDA-MB-231 breast cancer cells, SFN treatment cause dose-dependent and time-dependent inhibition of hTERT (human telomerase reverse transcriptase) via an epigenetic mechanism involving DNA methylation and histone modifications. SFN treatment was shown to cause downregulation of DNMT1 and DNMT3a, which induced site-specific demethylation at hTERT gene first exon facilitating the binding of CTCF associated with hTERT repression. Furthermore, ChIP analysis of hTERT promoter revealed that active histone chromatin marks such as acetyl-H3, acetyl-

H3K9 and acetyl-H4 were increased whereas repressive chromatin marks which include trimethyl-H3K9 and trimethyl-H3K27 were reduced after SFN treatment in a dose-dependent manner. The SFN induced hyper-acetylation was reported to promote the binding of repressor proteins such as MAD1 and CTCF to the hTERT regulatory region. In another study, Myzak et al. [196] reported that SFN metabolites–SFN–cysteine and SFN-N-acetylcysteine were more potent HDAC inhibitors *in vitro* as compared to SFN or its glutathione conjugate. Furthermore, SFN treatment in HCT116 human colorectal cancer cells increased β-catenin-responsive reporter (TOPflash) activity in a dose dependent manner and inhibited HDAC activity. Consequently, there was an induction in acetylated histone levels bound to p21/waf1 promoter. In human prostate epithelial BPH-1, LNCaP and PC-3 cells, SFN treatment was shown to inhibit HDAC activity, which was accompanied by an increase in acetylated histone levels by 50–100% and a corresponding induction of p21 and Bax expression which lead to downstream events such as cell cycle arrest and apoptosis [197]. In human breast cancer cells, SFN treatment was shown to inhibit HDAC activity but no change in H3 or H4 acetylation was observed [198]. In a recent study, Wong et al. [199] demonstrated the genome wide effects of SFN and DIM on promoter methylation in prostate epithelial as well as cancer cells using methyl-DNA immunoprecipitation followed by genome-wide DNA methylation array. The study reported SFN and DIM treatment induce widespread changes in promoter methylation patterns and reverse the status of several cancer-associated aberrantly methylated genes. SFN enhanced the nuclear translocation of Nrf2 and increased the mRNA and protein levels of the Nrf2 target genes in 12-O-tetradecanoylphorbol-13-acetate (TPA) in mouse skin epidermal JB6 (JB6 P+) cells [200]. Furthermore, SFN reduced the expression of DNMTs and downregulated the expression of HDAC-1, HDAC-2, HDAC-3 and HDAC-4, thereby reactivating Nrf2, a transcription factor for anti-oxidant enzymes. Another recent study by Mileo and Miccadei [201] highlighted the role of SFN and its metabolites sulforaphane-N-acetylcysteine (SFN-NAC) and sulforaphane-cysteine (SFNCys) generated via the mercapturic acid pathway in inducing acetylation of histones and inhibiting HDAC activity in the ileum, colon, and prostate C57BL/6J mice tissues. Another study by Myzak et al. [202] provided first evidence for inhibition of *in vivo* HDAC activity and suppression of tumorigenesis in APC-minus mice. Further studies demonstrated that daily SFN dose (7.5 μM per animal for 21 days) in the diet significantly reduced the growth of PC-3 cells in male nude mice, which correlated with a decrease in HDAC activity and increased global acetylation levels. Furthermore, in human subjects, single dose of 68 g broccoli sprouts caused a significant decrease in HDAC activity in peripheral blood mononuclear cells within 3–6 h after consumption [203].

4.0 Conclusion, limitation and future direction

The role of dietary phytochemicals as epigenetic modifiers has been well supported by the studies described herein holding great promise in cancer prevention and/or therapy. In addition, this review article provides a comprehensive summary on dietary phytochemicals with potential beneficial effects may in part be attributable to their epigenetic properties, including changes in DNA methylation patterns, histone modifications, and in the expression of miRNAs (Figure 1). The fundamental role of epigenetic mechanisms in the regulation of gene expression and epigenetic aberrations implicated in various pathologies itself

underlines the importance of compounds targeting them. It is much more challenging than it seems to develop dietary phytochemicals as effective chemopreventive and/or chemotherapeutic agents despite their widespread recognition and acceptance as evident from a large number of research publications [204–258]. There is still insufficient preclinical and clinical data published on the epigenetic changes induced by some of the dietary polyphenols, which remains a challenge and limitation, of the current data to acquire better insight on the molecular mechanisms responsible for these effects. The next important step would be to determine the most effective doses of these dietary phytochemicals in order to obtain beneficial effects in humans. The doses provided in most of the cell culture studies and *in vivo* experiments remains pharmacologically irrelevant as such high concentrations of these compounds may not be achieved in humans, and might lack clinical benefit. As such, pre-clinical and clinical studies addressing the relevance and validity of *in vitro* experimental outcomes as well as analysis of safety profile, dose, bio-availability and routes of administration for these compounds are required for designing better chemopreventive/therapeutic strategies along with appropriate designing of the clinical trial. Based on profound research interest in the emerging area of epigenetics with dietary phytochemicals several directions in future could be pursued:

1. Epigenetic remedy with dietary phytochemicals is an emerging area of research that could be effective and valuable approach in fighting cancer at the level of gene expression. Studies conducted to date have shown significant effects from many dietary compounds that target epigenetic pathways in preventing cancer and additional mechanistic studies are needed, in particular, with untested dietary agents.
2. The exciting field of epigenetics and nutrigenomics, in particular, addresses how nutrients affect the epigenome by targeting DNA methylation, HDAC activity and miRNAs having chemopreventive potential. The effect of a combination of dietary phytochemicals, their course of action and targets is still at an early stage and could be a promising strategy for epigenetic studies.
3. The phenotype as a result of complex gene-environment interactions in the current, past and ancestral environment results in lifelong remodeling of the epigenome. As some of the effects of these dietary phytochemicals appear to be cell type or organ specific therefore, understanding the mechanism(s) of these differences is a key in designing a personalized regimen for cancer prevention and/or cure.
4. Several studies have demonstrated that disruption of epigenetic mechanisms can alter immune function and contribute to various disease phenotypes. Understanding and manipulating the epigenome with dietary phytochemicals with a focus on modulating DNA and histone methylation of key inflammatory genes is an effective approach to target immune-related pathways.
5. Epigenetic defects may eventually lead to genetic defects which are not reversible, appropriate time of interventions using dietary phytochemicals

which might be effective in slowing and/or reversing cancer progression should be pursued as future research.

6. It is demonstrated that nanomaterials encapsulation technology enhances bioavailability and offers significant promise for chemoprevention. Attempts have been made encapsulating various dietary phytochemicals such as curcumin, resveratrol, EGCG and genistein in nanoparticles to circumvent the issues of poor bioavailability with dietary agents, and may be considered for epigenetic studies.

7. Studies have highlighted the existence of cancer stem cells in most solid and nonsolid tumors. These cells are considered responsible for tumor relapse and resistance to therapy. It has been shown that dietary phytochemicals can impact cancer stem cell self-renewal related pathways. Additional epigenetic studies are needed to determine the pathways which are altered by this particular pool of cancer stem cells.

In conclusion, our knowledge regarding nutritional and diet-based epigenetics is still limited. In particular, the effects of nutrients or bioactive food components on DNA methylation, miRNA expression histone methylation or chromatin remodeling complexes are largely unknown. In future, with the emergence of novel technologies such as next generation sequencing for the genome-wide assessment of DNA methylation, localization of the histone marks, and development of bioinformatics tools to systematically integrate information can facilitate the analysis of epigenetic studies with dietary phytochemicals.

Acknowledgments

The original work from author's laboratory outlined in this review was supported by VA Merit Review 1I01BX002494 and from the United States Public Health Service Grants RO1CA108512, R21CA193080 and R03CA186179 to SG.

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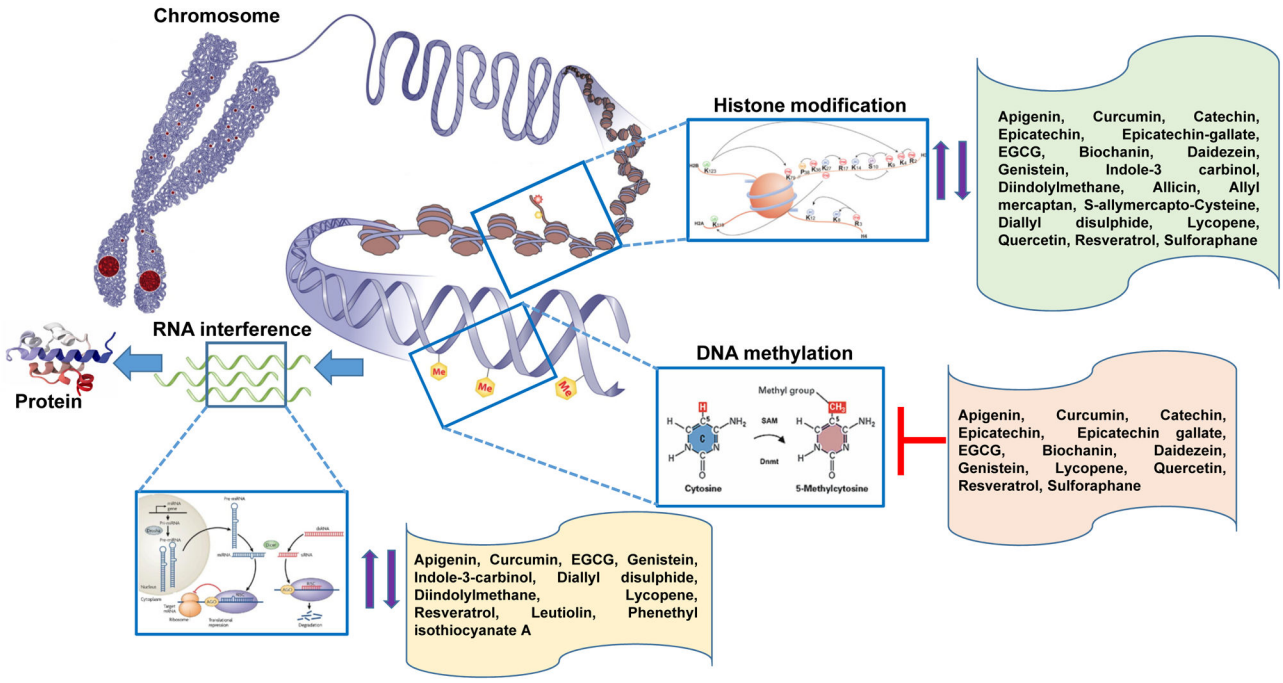
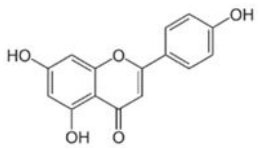
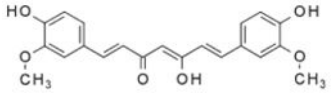
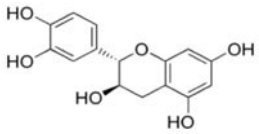
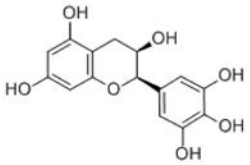
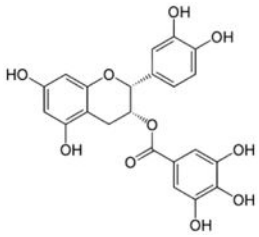
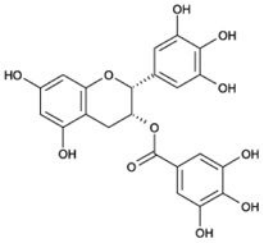


Figure 1.

Overview of epigenetic mechanisms regulating gene expression. Dietary phytochemicals impart anticancer properties through alteration in DNA methylation patterns, histone modification, and changes in non-coding (micro) RNAs levels. Up and down, *arrows* and ⊢ inhibition.

Table 1

Structure, IUPAC name and molecular weight of some common dietary phytochemicals.

Dietary Agent	Structure	IUPAC Name
Apigenin		5,7-dihydroxy-2-(4-hydroxyphenyl)chromen-4-one
Curcumin		(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
Green tea polyphenols		
Epicatechin		(2R,3R)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol
Epigallocatechin		(2R,3R)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol
Epicatechin gallate		[(2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzo
Epigallocatechin gallate		[(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxyber
Soy isoflavones		

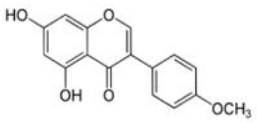
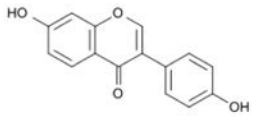
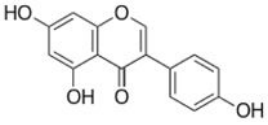
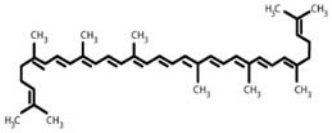
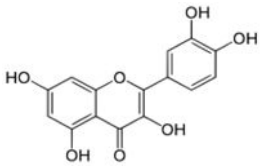
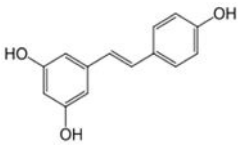
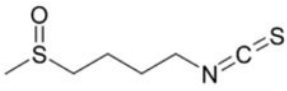
Dietary Agent	Structure	IUPAC Name
Biochanin A		5,7-dihydroxy-3-(4-methoxyphenyl)chromen-4-one
Daidezein		7-hydroxy-3-(4-hydroxyphenyl)chromen-4-one
Genistein		5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one
Lycopene		(6E,8E,10E,12E,14E,16 E,18E,20E,22E,24E,26E)-2,6,10,14,19,23,27,31-octamethyldotriaconta-2,6,8,1
Quercetin		2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one
Resveratrol		5-[(E)-2-(4-hydroxyphenyl)ethenyl]b enzene-1,3-diol
Sulforaphane		1-isothiocyanato-4-methylsulfinylbutane

Table 2

Dietary phytochemicals altering DNA methylation.

Dietary Phytochemical	Molecular mechanism(s)	Target genes	Preclinical Model	Disease Type	Dose/Concentration	Ref.
Apigenin	DNMT inhibitor	NA	Esophageal cells	NA	20–50 μM	85
	DNMT inhibitor	Decreases CpG hypermethylation in Nrf2 promoter	Skin cancer (mouse skin)	Cancer	(1.56–50 μM)	87
Curcumin	DNMT inhibitor	NA	Esophageal Leukemia	Cancer	3–50 μM	85
Catechin	DNMT inhibitor	*RARβ*	Breast		5–50 μM	204
Epicatechin	DNMT inhibitor		Breast		50 μM	204, 113
Epicatechin-gallate	DNMT inhibitor		Esophageal		20–50 μM	204, 113
Epigalocatechin-3-gallate	DNMT inhibitor	*RARβ, MGMT, MLH1, CDKN2A, RECK,TERT, RXRα,CDX2, GSTP1, W1F1*	Esophageal, Oral, Prostate, Lung, Colon cancer cells	Cancer	20–100 μM: 0.3–06%	109, 205, 206, 207, 208
Biochanin A	DNMT inhibitor	NA	Esophageal, Prostate	Cancer	20–100 μM	85,
Daidezein	DNMT inhibitor	NA	Breast		20–40 μM	113, 124, 126
Genistein	DNMT inhibitor	*RARβ, MGMT, CDKN2A, GSTP1, HMGNS, BTG3 RXRα, CDX2, GSTP1, W1F1*	Esophageal Prostate Tumors (Mice)		50–300 mg/kg 3.75–100 μM	85, 124, 126, 127, 128, 129, 131, 135, 209, 210, 211
Lycopene	Unknown	*GSTP1, RARβ, HIN-1*	Breast	Cancer	2 μM	126
	DNMT inhibitor	*Activation of GSTP1 promoter*	Prostate		5–40 μM	
Quercetin	DNMT inhibitor	*CDKN2A*	Esophageal Breast Colon	Cancer	5–20 μM	165
Resveratrol	DNMT inhibitor	NA	Breast, Lungs	Cancer	20–40 μM	212, 213
Sulforaphane	DNMT inhibitor	NA	Esophageal, Colon	Cancer	50 μM	212

NA, information not available

Table 3

Dietary phytochemicals and histone modification.

Dietary Agent	Molecular mechanism(s)	Target genes	In vitro model	In vivo model	Disease Type	Dose/Concentration	Ref.
Apigenin	HDAC inhibitor	*p21*	PC-3 cells	Mouse xenograft	Prostate cancer	20–50 μM (20–50 μg/day)	86
	HDAC inhibitor	NA	Skin cancer cells (mouse)			1.56–50 μM	87
Curcumin	HAT & HDAC inhibitor	H3/H4 deacetylation GATA4, EOMES, GZMB, PRF1	Cervix, HIV, Hepatoma Leukemia, Prostate Brain, Lymphoma	Plasmodium falciparum; Herpes Virus Mouse: Rat	Malaria Herpes Epilepsy Diabetes and Heart failure	0.3–75mg/kg (6.25–135μM)	96–106 214–222
Catechin	HAT inhibitor	NA	Lymphocytes	NA		100 μM	223
Epicatechin	HAT inhibitor	NA	Lymphocytes	NA		100 μM	223
Epicatechin-gallate	HAT inhibitor	NA	Lymphocytes, Colon	NA		100 μM	223
Epigallocatechin-3-gallate	HAT inhibitor	H3/H4 acetylation	Lymphocytes, Colon	NA	Cancer	5–100 μM	223
	HMT inhibitor	H3K27 trimethylation *NF-κB, IL-6, BMI-1, EZH2, SUZ12*	Keratinocytes, Prostate	NA			
Equol	HDAC inhibitor	H2A/H2B/H3/H4	Drosophila	NA		12.8 μM	130
Genistein	HAT inhibitor	Acetylation H2A/H2B/H3/H4	Esophageal; Prostate, Breast, Renal	NA	Cancer	5–100 μM	124, 127, 128, 130, 131,
	HADC inhibitor	Acetylation *p21, p16, PTEN, p53 FOXA3, SIRT1, hTERT*		NA			
Daidzein	HDAC inhibitor	Histone acetylation	Esophageal, Prostate	NA	Cancer	12.8–100 μM	130, 210
Indole-3 carbinol Diindolylmethane	HDAC inhibitor	IFN-γ, TNF-α, IL-6, IL-2, NF-κB, COX-2, iNOS, IL-1β, IL-12	Prostate cancer	Sprague-Dawley rats		20–80 μg/rat	82, 141, 143–150
			Colon Cancer	Nude mice	Cancer	15–100 μM	
			Spleenocytes (CD3+ cells)	Nude mice		15–100 μM 100–300 mg/kg 100 μM	

Dietary Agent	Molecular mechanism(s)	Target genes	In vitro model	In vivo model	Disease Type	Dose/Concentration	Ref.
						40 mg/kg	
Allicin	unknown	H4 acetylation	Erythroleukemia	NA		2–200 μM	157–159
Allyl mercaptan	SIRT1 inhibitor	H3/H4 acetylation P21/WAF1	Erythroleukemia Liver, Colon	Rat: liver	Cancer	2–500 μM (100mg/kg)	157–159, 224
S-allymercapto-Cysteine	HAT inhibitor	H3/H4 acetylation	Erythroleukemia	NA		20–250 μM	156, 161
Diallyl disulphide	HDAC inhibitor	H3/H4 acetylation P21/WAF1	Erythroleukemia, Leukemia, Liver, Colon, Prostate, Fibroblast	Rat	Cancer	20–200 μM (42–200 mg/kg)	156–159,161 224
Quercetin	SIRTI activator HAT inhibitor	*IP-10, MIP-2*	Cervix, Drosophila Small intestine	Cancer Mouse Bowel inflammation	Inflammatory diseases	100 μM	164–175, 181,182
Resveratrol	SIRTi activator	*TNF-α, IL-8, RBP*	Cervix, Endothelial Embryonic kidney, Macrophages, Lungs, Liver, Cardiomyocytes	Yeast, Drosophila Mouse Rats	Colon cancer Lung cancer	10–200 μM	177–191
Sulforaphane	HDAC inhibitor	H3/H4 acetylation *RARβ, HBD-2, p21, Bax*	Prostate, Breast, Colon, Kidney	Mouse, prostate cancer xenografts	Cancer	15–25 μM (443 μg/kg, 68g)	193–203, 225–227

NA, information not available

Table 4

Dietary phytochemicals and changes in miRNA levels.

Dietary Agent	Disease Type	miRNA	Concentration	Ref.
Apigenin	Lung cancer cells	miR138, miR-125a-5p	25–100μM	230
	Neuroblastoma cells	miR-138	100 μM	229
Curcumin	Bladder cancer cells	miR-203	1–20 μM	231
	Lung cancer cells	miR-320, miR-26a, let-7i, miR-130a, mir-16, miR-125b,miR-23a, miR-27b, miR-155, miR-625, miR-576-3p, miR-186, miR-9	10–50 μM	232
	Leukemia	miR-15a, miR-16-1	5–20 μM	233
	Pancreatic cancer cells	miR-103, miR-140, miR-146b, miR-148, miR-15b,miR-181a, miR-181b, miR-181d, miR-195, miR-196a,miR-199a, miR-19a,miR-204, miR-20a, miR-21, miR-22miR-23a,b, miR-24, miR-25, miR-26a, miR-27a, miR-34a,miR-374, miR-510, miR-7, miR-92, miR-93, miR-98	10 μmol/L	234
EGCG	Neuroblastoma cells	miR-92, miR-93,miR 106b, miR-34a, miR-99a	25–100 μM	228
	Hepatocellular carcinoma cells	miR-467b, miR-487b, miR-197, miR-805, miR-374, let-7f, miR-350, miR-24-1, miR-137, miR-335-3p, let-7a, miR-222, miR-26b, miR-30c-1, let-7d, miR-98, miR-30c, miR-30b, miR-32, miR-674, miR-532-5p, let-7g, miR-18a, miR-192, miR-302d, miR-30b, miR-802, let-7e,miR-322, miR-720, miR-146b, miR-340-3p, miR-185, miR-425, miR-10a, miR-126-5p, miR-101a, miR-30e, let-7c, miR-141, miR-33, miR-29a, miR-199b, miR-450a-5p, miR-21, miR-23a, miR-101b, miR-148a, miR-193, miR-23b, miR-107, miR-140, miR-551b, miR-466c-5p, miR-106a, miR-590-3p, miR-875-3p, miR-224, miR-292-5p, miR-678, miR-469, let-7b, miR-463miR-574-3p, miR-201, miR-290-3p, miR-181a, miR-302a, miR-429, miR-133a, miR-190b, miR-710, miR-135b, miR-296-5p, miR-191, miR-188-5p, miR-298, miR-181a-1, miR-466g, miR-26b, miR-466f-3p, miR-29b, miR-1224, miR-291b-5p, miR-324-5p, miR-486, miR-128, miR-450b-3p, miR-135a, miR-294, miR-671-5p, miR-878-3p, miR-801, miR-370, miR-1, miR-494, miR-133b	100 μM	235
	Lung carcinoma	let-7c, miR210	100 μM	235
	Pancreatic cancer cells	let-7c	100 μM	235
	Colon carcinoma cells	miR-27a, miR-20A, miR-17-5P, miR-21	5–30 μM	236
Genistein	Ovarian cancer cells	miR-100, miR-122a, miR-125b, miR-126, miR-135, miR-135b, miR-136, miR-137, miR-141, miR-152,miR-190, miR-196a, miR-196b, miR-204, miR-205, miR-206, miR-217, miR-22, miR-296, miR-30a-3p, miR-30a-5p, miR-331, miR-335, miR-342, miR-362, miR-449b, miR-454, miR-497, miR-500, miR-501, miR-503, miR-515, miR-517c, miR-532, miR-565, miR-578, miR-584, miR-585, miR-590, miR-595, miR-625, miR-647, miR-7, miR-765, miR-766	5 μM	136
	Pancreatic cancer cells	miR-200	50 μM	137

Dietary Agent	Disease Type	miRNA	Concentration	Ref.
Indole-3 carbinol Diindolylmethane	Breast cancer cells	miR34a	25 μM	137
	Prostate cancer cells	miR34a	10 μM	238
		miR-21	30–60 μM for cells 5mg/kg (mice)	237
	Mouse lung tumors	miR-21, mir-31, miR-130a, miR-146b and miR-377	100–150 μM	239
Lycopene	Hepa 1–6 cells (hepatic cells)	miR-21	0.05% (fed orally to mice)	240
Diallyl disulphide	Endothelial progenitor cells	miR-221	0–10 μM (10mg/kg/day)	241
	Breast Cancer	miR34a	25–400 μM	242
Resveratrol	Prostate cancer cells from lymph node	miR-1224-5p, miR-1228, miR-1231, miR-1246, miR-1260, miR-1267, miR-1268, miR-129, miR-1290, miR-1308, miR-1469, miR-149, miR-150, miR-152, miR-15a, miR-17, miR-1825, miR-185, miR-18b, miR-1908, miR-1915, miR-197, miR-1972, miR-1973, miR-1974, miR-1975, miR-1977, miR-1979, miR-20a, miR-20b, miR-24, miR-296-5p, miR-483-5p, miR-513a-5p, miR-548q, miR-572, miR-575, miR-612, miR-638, miR-654-5p, miR-659, miR-671-5p, miR-7, miR-762, miR-764, miR-874, miR-92b, miR-939	50 μM	243
	Prostate cancer cells	miR-101, miR-106a, miR-106b, miR-1274b, miR-136, miR-141, miR-145, miR-17, miR-182, miR-1826, miR-200b, miR-200c, miR-20a, miR-20b, miR-21, miR-214, miR-221, miR-222, miR-302c, miR-375, miR-378, miR-720, miR-768-3, miR-93	5–100 μM	244
	Colorectal cancer cells	miR-1, miR-100-1/2, miR-102, miR-103-1, miR-103-2, miR-146a, miR-146b-5p, miR-16-0, miR-17, miR-181a2, miR-194-2, miR-196a1, miR-205, miR-206, miR-21, miR-23a, miR-23b, miR-25, miR-26a, miR-29c, miR-30a-3p, miR-30c-1, miR-30d, miR-30e-5p, miR-323, miR-340, miR-363-5p, miR-424, miR-494, miR-497, miR-560, miR-560, miR-565, miR-565, miR-572, miR-574, miR-594, miR-615, miR-622, miR-629, miR-631, miR-638, miR-639, miR-657, miR-659, miR-663, miR-801, miR-92a-2	50 μM	245
Luteolin	Prostate cancer cells	miR-630	0–10 μM	246
	Gastric cancer cells	miR-34a	5–50 μM	247
Phenethyl isothiocyanate	Prostate cancer cells	miR-141	0–20 μM	248

Table 5

Clinical trials conducted with dietary phytochemicals.

Dietary Agent	Molecular mechanism	Disease conditions	Dose	Endpoints/Outcome	Ref.
Curcumin	DNMT inhibitor	Prostate cancer	0.1 g/day	Curcumin modulates PSA production in combination with other isoflavones	249
	DNMT inhibitor	Colorectal cancer	0.036–0.18 g/day	Pilot study shows safe administration in patients up to an equivalent dose of 180 mg. It has low bioavailability in humans and undergoes intestinal metabolism.	250
Catechin	DNMT inhibitor	Prostate cancer	NA	May decrease risk for advanced prostate cancer.	251
Epicatechin	DNMT inhibitor		25.5 mg	Studies finds low bioavailability and/or bioaccumulation of green tea polyphenols in prostate tissue with statistically insignificant changes in systemic and tissue biomarkers. Green tea polyphenol activity may be indirect or need evaluation with longer intervention durations, repeated dosing, or in patients at earlier stages of the disease.	252
Epicatechin-gallate	DNMT inhibitor		39.8 mg		
Epigalocatechin-3-gallate	DNMT inhibitor		200 mg		
Genistein	DNMT inhibitor	Prostate cancer	30 mg	Genistein intake by early prostate cancer patients modulates several biomarkers and has an inhibitory effect on androgen related biomarker.	253
	Decreases MBD1, MBD4, MeCP2 expression			May induce cell cycle arrest and inhibit proliferation	254
Daidzein	HDAC inhibitor	Prostate cancer	0.02 mg	Safety and tolerability of isoflavone intake are proven. The results support the value of isoflavone treatment for prostate cancer risk reduction.	254
Indole-3 carbinol	HDAC inhibitor	Prostate cancer	225 mg	BR-DIM was well tolerated in prostate cancer patients. Showed variable results on PSA levels.	255
Lycopene	DNMT inhibitor	Prostate cancer	20–25 μM	Prostatic lycopene levels were low after supplementation in prostate cancer patients and no change in rate of HGPIN progression to prostate cancer.	256
Quercetin	DNMT inhibitor	Renal cancer	1400 mg/m^2	Plasma levels of quercetin inhibited lymphocyte tyrosine kinase activity, with evidence of antitumor activity.	257
Sulforaphane	Decreases DNMT expression	Prostate cancer	200 μmoles/day	PSA levels were not affected significantly.	258

NA, information not available