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Review

Cancer chemoprevention by dietary polyphenols: Promising role for epigenetics

Alexander Link [a,b], Francesc Balaguer [a,c], Ajay Goel [a,*]

[a] Gastrointestinal Cancer Research Laboratory, Division of Gastroenterology, Baylor Research Institute and Charles A Sammons Cancer Center, Baylor University Medical Center, Dallas, TX, USA
[b] Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University, Magdeburg, Germany
[c] Department of Gastroenterology, Hospital Clinic, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), IDIBAPS, University of Barcelona, Spain

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ABSTRACT

Epigenetics refers to heritable changes that are not encoded in the DNA sequence itself, but play an important role in the control of gene expression. In mammals, epigenetic mechanisms include changes in DNA methylation, histone modifications and non-coding RNAs. Although epigenetic changes are heritable in somatic cells, these modifications are also potentially reversible, which makes them attractive and promising avenues for tailoring cancer preventive and therapeutic strategies. Burgeoning evidence in the last decade has provided unprecedented clues that diet and environmental factors directly influence epigenetic mechanisms in humans. Dietary polyphenols from green tea, turmeric, soybeans, broccoli and others have shown to possess multiple cell-regulatory activities within cancer cells. More recently, we have begun to understand that some of the dietary polyphenols may exert their chemopreventive effects in part by modulating various components of the epigenetic machinery in humans. In this article, we first discuss the contribution of diet and environmental factors on epigenetic alterations; subsequently, we provide a comprehensive review of literature on the role of various dietary polyphenols. In particular, we summarize the current knowledge on a large number of dietary agents and their effects on DNA methylation, histone modifications and regulation of expression of the non-coding miRNAs in various *in vitro* and *in vivo* models. We emphasize how increased understanding of the chemopreventive effects of dietary polyphenols on specific epigenetic alterations may provide unique and yet unexplored novel and highly effective chemopreventive strategies for reducing the health burden of cancer and other diseases in humans.

Contents

Abbreviations: DNMT, DNA methyltransferase; HMT, histone methyltranferase; HDAC, histone deacetylase; HAT, histone acetyltransferase; DIM, 3,3′-diindolylmethane; SGR, sanguinarine; SAM, S-adenosyl methionine; SAH, S-adenosyl-L-homocysteine; miRNA, microRNA; EGCG, epigallocatechin-3-gallate; PsA, psammaplin A; SFN, sulforaphane; AM, allyl mercaptan; DADS, diallyl disulfide; COPD, chronic obstructive pulmonary disease; PEITC, phenethyl isothiocyanate; EMT, epithelial-mesenchymal transition; LINE, long interspersed nuclear elements; 5-aza-CdR, 5-aza-2-deoxycytidine; TSA, trichostatin A.

* Corresponding author at: Gastrointestinal Cancer Research Laboratory, Baylor University Medical Center, 3500 Gaston Ave, Suite 250 Hoblitzelle, Dallas, TX 75246, USA. Tel.: +1 214 820 2692; fax: +1 214 818 9292.
E-mail address: ajay.goel@baylorhealth.edu (A. Goel).

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1. Introduction

1.1. Epigenetics and cancer

Cancer is widely perceived as a heterogeneous group of disorders, which is caused by a series of clonally selected '*genetic*' changes in key tumor suppressor genes and oncogenes. However, accumulating evidence in the recent years indicate that tumor cell heterogeneity is in part due to significant contribution of '*epigenetic*' alterations in cancer cells. Consequently, it is now becoming apparent that epigenetic plasticity together with genetic lesions drives tumor progression, and that cancer is the manifestation of both genetic and epigenetic modifications [1–4]. Although a small proportion of tumors can be inherited, it is believed that majority of cancers result from changes that accumulate throughout the life because of exposure to various endogenous factors such as nutrients, infections, physical activity, social behavior and other environmental factors. Even when cancer initiation and progression is driven by acquired genetic alterations, epigenetic disruption of gene expression plays an equally important role in the development of disease [5], and arguably diet and environment-mediated epigenetic perturbations play a crucial role in cancer progression in humans [6–8].

The term 'epigenetics', which was first coined by the developmental biologist Conrad H. Waddington in 1942, is defined as *reversible* heritable changes in gene expression that occur without alteration in DNA sequence, but changes that are sufficiently powerful to regulate the dynamics of gene expression [9]. Three distinct and intertwined mechanisms are known to be part of the "epigenome", which includes DNA methylation, histone modifications, and post transcriptional gene regulation by non-coding microRNAs (miRNAs) [2]. These processes affect transcript stability, DNA folding, nucleosome positioning, chromatin compaction, and complete nuclear organization of the genetic material (Figure 1). Synergistically and cooperatively they determine whether a gene is silenced or expressed, as well as the timing and tissue-specificity of the expression of these genes. Disruption of the epigenome certainly underlies disease development. Therefore, disease susceptibility is clearly a result of complex interplay between one's genetic endowment and epigenetic marks imprinted on one's genome by endogenous and exogenous factors [10].

From a clinical point of view, epigenetics offers a very promising and attractive avenue. This is because, unlike genetic changes (mutations, gene deletions, etc.), epigenetic alterations are potentially reversible. What this means is that unlike mutations, which exist for the lifetime, epigenetically modified genes can be restored; methylation silenced genes can be demethylated, and histone complexes can be rendered transcriptionally active by modification of acetylation and methylation of various histones via nutrients, drugs and other dietary interventions. This is really fascinating, as this provides a perfect opportunity for designing optimal chemopreventive and therapeutic strategies. The mechanism of interaction between various epigenetic factors and regulation of chromatin structure, dynamics, and ultimately gene expression is an active area of research, and recent understanding of these epigenetic mechanisms is highlighted in the sections below.

1.1.1. DNA methylation

DNA methylation of cytosines at CpG dinucleotides is perhaps the most extensively studied epigenetic modification in mammals. DNA methylation, in association with histone modifications is an essential component of the epigenetic machinery, which regulates

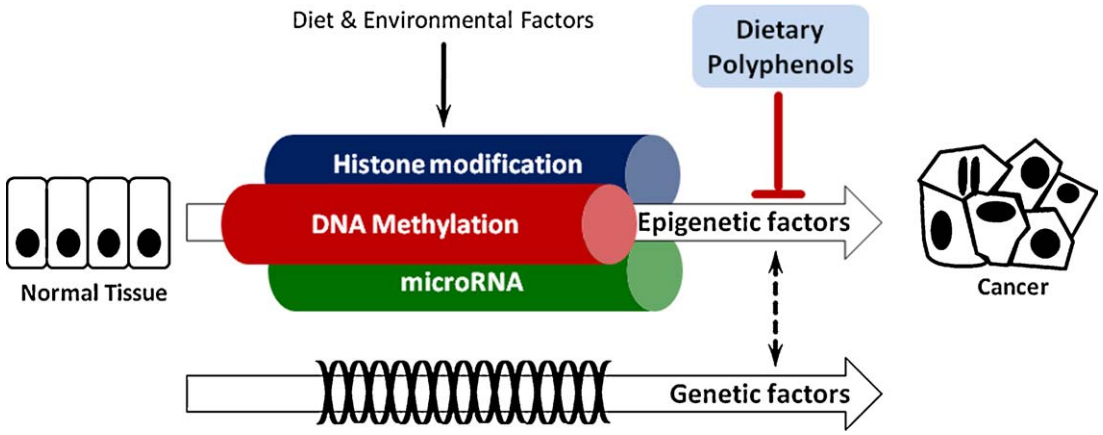

Fig. 1. Epigenetic mechanisms involved in carcinogenesis. Carcinogenesis is a long-term process and both genetic and epigenetic factors contribute to cancer development. Epigenetic changes, such as DNA methylation, histone modifications and microRNAs are easily influenced by dietary and environmental factors. Dietary polyphenols can potentially impact all three epigenetic modifications, which in turn contribute towards their chemopreventive potential.

gene expression and chromatin architecture [11]. In mammalian cells, DNA methylation occurs at the 5′ position of the cytosine residues within CpG dinucleotides through addition of a methyl group to form 5-methylcytosine [12]. CpG dinucleotides are not uniformly distributed throughout the human genome, but are often enriched in the promoter regions of genes, as well as regions of large repetitive sequences (e.g. centromeric repeats, LINE and ALU retrotransposon elements) [13]. Short CpG-rich regions are also called as "CpG islands", and these are present in more than 50% of human gene promoters [14]. Whilst most of the CpG dinucleotides in the genome are methylated, the majority of CpG islands usually remain unmethylated during development and in undifferentiated normal cells [15]. Hypermethylation of CpG islands within gene promoters can result in gene silencing, while promoters of transcriptionally active genes typically remain hypomethylated [15]. DNA methylation can lead to gene silencing by either preventing or promoting the recruitment of regulatory proteins to DNA. For example, it can inhibit transcriptional activation by blocking transcription factors from accessing target-binding sites, e.g. c-myc [16]. In other instances, it can provide binding sites for methyl-binding (sequestering) domain proteins, which can orchestrate gene repression through interaction with histone modifying enzymes [17]. Thus DNA methylation uses a variety of mechanisms to silence genes, and a direct association between DNA methylation and the phenotype of a cell can be postulated.

The modification at 5-methylcytosine is catalyzed by various DNA methyltransferases (DNMTs). There are three main DNMTs; DNMT1, which is the major maintenance enzyme that preserves existing methylation patterns following DNA replication by adding methyl groups to the hemi-methylated (partially-methylated) CpG sites [18,19]; DNMT3a and DNMT3b on the other hand serve as *de novo* methyltransferases, which act independent of replication and show equal preference for both unmethylated and hemi-methylated DNA [20,21]. The role of DNA methylation-induced transcriptional silencing of genes is now well-established in multiple human malignancies [22]. In fact, analogous to mutations and deletions, DNA methylation of genes in most human cancers is now believed to be a most frequent mechanism for the transcriptional silencing of tumor suppressor genes [23]. Several detailed and informative reviews on the association between DNA methylation and cancer are available, but these are beyond the scope of this review [11,19,24–27].

1.1.2. Histone modifications

In addition to direct methylation of DNA, chromatin structure is frequently influenced by diverse histone modifications, which also play an important role in gene regulation and tumorigenesis [3,4]. Chromatin proteins serve as building blocks to package eukaryotic DNA into higher order chromatin fibers. Each nucleosome encompasses ~146 bp of DNA wrapped around an octamer of histone proteins. These octamers consist of double subunits of H2A, H2B, H3 and H4 core histone proteins [28]. The histone proteins coordinate the changes between tightly packed DNA (or heterochromatin), which is inaccessible to transcription, and lightly packed DNA (or euchromatin), which is available for active transcription through binding of transcription factors [29]. These changes typically occur in the 'histone tails', which extend from the core octamer. The histone tails comprise of a globular C-terminal domain and an unstructured N-terminal tail [30]. The N-terminal histone tails are the major sites for post-translational modifications including methylation, acetylation, phosphorylation, ribosylation, ubiquitination, sumoylation and biotinylation [31]. The majority of these modifications take place at lysine, arginine and serine residues within the histone tails and regulate key cellular processes such as transcription, replication and repair [31]. Unlike DNA methylation, histone modifications can lead to either activation or repression depending upon which residues are involved, and the type of modification present. For instance, lysine acetylation associates with transcriptional activation, while its methylation leads to transcriptional activation or repression depending upon which specific lysine is modified. For instance, tri-methylation of lysine 4 on histone H3 (H3K4me3) is enriched at transcriptionally active gene promoters [32], whereas tri-methylation of H3K9 (H3K9me3) and H3K27 (H3K27me3) is present at transcriptionally repressed promoters [31]. H3K9me3 and H3K27me3 histone modifications together constitute the two main silencing mechanisms in mammalian cells.

Similar to DNA methylation changes, various histone modifications are potentially reversible, and are dynamically regulated by groups of enzymes that add or remove covalent modifications to histone proteins [3,33]. Histone acetyltransferases (HATs) and histone methyltransferases (HMTs) add acetyl and methyl groups, respectively, whereas histone deacetylases (HDACs) and histone demethylases (HDMs) remove acetyl and methyl groups, respectively, from histone proteins [34–36]. A number of histone-modifying enzymes including various HATs, HMTs, HDACs, and HDMs have been identified in the recent years, including a large number of dietary polyphenols enumerated in the later sections of this review.

1.1.3. microRNAs

Besides DNA methylation and histone modifications, miRNAs are emerging as key mediators of epigenetic gene regulation in

mammals. Non-coding RNAs, including miRNAs, were initially noted to perform catalytic functions in facilitating RNA splicing. In recent years it has been recognized that they participate in the post-transcriptional gene regulation [37,38]. miRNAs are small single-stranded RNAs, ~19–24 nucleotides in length, that regulate gene expression through post-transcriptional silencing of the target genes. Sequence specific base pairing of miRNAs with 3′ untranslated regions of the target messenger RNA (mRNA) results in degradation or translational inhibition [39]. miRNAs are expressed in a tissue-specific manner and control a wide spectrum of biological processes including cell proliferation, apoptosis and differentiation. Although miRNA are vital to normal cell physiology, aberrant expression of these small non-coding RNAs has been linked to carcinogenesis. In fact, miRNA profiles are now being used to classify human cancers [40–42]. One of the interesting features of miRNAs is that similar to regular genes, their own expression can be regulated by other epigenetic mechanisms, such as DNA methylation [43]. The influence of miRNA on the epigenetic machinery and the reciprocal epigenetic regulation of miRNA expression suggest that its deregulation during carcinogenesis has an important implication for global regulation of epigenetics and cancer. Additionally, interaction among various components of the epigenetic machinery re-emphasizes the integrated nature of epigenetic mechanisms involved in the maintenance of global gene expression patterns in mammals. Several detailed and informative reviews of the association between miRNA and cancer have been published previously [37,41,44–46].

2. Dietary and environmental factors and their influence on epigenetics

Perhaps one of the most interesting and important features of epigenetics and its role in disease development is the fact that, unlike genetic changes, epigenetic marks can be modified by the environment, diet or pharmacological intervention. This feature of epigenetic modifications has fueled enthusiasm for developing therapeutic strategies by targeting the activity of various epigenetic factors, such as DNMTs and HDACs, in order to prevent or treat various disease including human cancers [47,48]. Next, we will briefly focus on the historical and current evidence for interactions between the environment, nutrition and the "epigenome", and the rationale for chemoprevention and therapy using dietary factors.

2.1. Nutrient deficiency and human cancer

Nutrients like folic acid, B vitamins and SAM (S-adenosyl methionine) are key components of the methyl-metabolism pathway, and methyl-donating nutrient-rich diet can rapidly alter gene expression, especially during early development when the epigenome is first being established. As a result, diet can influence the degree of methylation by modifying the availability of methyl donors, including folate, choline, and methionine, as well as DNMT activity [49–53]. A classic example of the dietary influence on DNA methylation and cancer is the finding that dietary methyl deficiency (of folate, choline, and methionine) in an animal model was shown to alter hepatic DNA methylation patterns and induce liver cancer in the absence of a carcinogen [54]. A more recent study revealed that only with early re-feeding of a methyl-sufficient diet during methyl-deficiency-induced hepatocarcinoma in mice can help mitigate aberrant DNA methylation defects, emphasizing that timing must to be considered in any intervention [55].

Selenium is another nutrient that has been linked with DNA methylation, both in cultured cell studies and animal experiments. It was demonstrated that in rats fed with selenium-rich diets, both liver and colon DNA were significantly hypomethylated, thus providing a rationale for their potential chemopreventive efficacy [52,56]. These effects of selenium were linked to its ability to inhibit DNMT1 activity and decreased DNMT1 protein expression [56].

2.2. Agouti mice

Classical experiments in mice show just how important a mother's diet is in shaping the epigenome of her offspring. At present, the best evidence to demonstrate that nutrition can modulate the epigenetic status of mammals comes from studies with mice carrying the agouti viable yellow (*Avy*) gene. The normal function of the *Avy* gene is to confer a wild-type coat color. However, dominant mutations at the agouti locus cause a pleiotropic syndrome, which confers excessive amounts of yellow pigment on the coat, together with systemic effects including obesity, a non-insulin-dependent diabetic-like condition, and of vulnerability to various types of cancer [57]. In the *Avy* mouse, the expression of the allele varies with its methylation status, and when methylated, the gene behaves like a wild type allele and is expressed only in the hair follicle. When unmethylated, the gene is expressed ubiquitously, causing the full agouti syndrome. However, intermediate levels of methylation cause a mottled appearance, so that the coat color and other aspects of the agouti phenotype provide a direct readout of the methylation status of the allele. Using this model, Wolff and colleagues showed that by feeding diets supplemented with high levels of folic acid (as methyl donor) to pregnant dams it was possible to modify the expression of the agouti gene in the offspring [58]. A higher proportion of offspring with wild type coat color were obtained from supplemented dams, which was consistent with higher levels of DNA methylation of the agouti gene [59,60]. One of the most remarkable features of the *Avy* mouse model is that there is good evidence that the epigenetic marks established by dietary supplementation with methyl donors can be passed to a successive generation via the female germline and that these effects are mediated by polycomb group proteins [61]. These results indicate that an individual's adult health is heavily influenced by early prenatal factors, and that our health is not only determined by what we eat, but also what our parents ate.

2.3. Maternal behavior and epigenetic changes in animals

Till date, there are not many well-authenticated examples of direct effects of the environment on epigenetic status in mammals, but one of the remarkable examples is the effect of maternal care behavior on the offspring of rodents. In a very interesting study, it was demonstrated that high levels of pup-licking, grooming and "arched-back nursing" by rat mothers modified the levels of DNA methylation at a glucocorticoid receptor (GR) gene promoter in the hippocampus of the offspring, leading to altered histone acetylation and binding of a transcription factor (NGFI-A) to the GR promoter [62]. Remarkably, central infusion of a histone deacetylase (HDAC) inhibitor abolished the group differences in histone acetylation, DNA methylation, NGFI-A binding, expression of the GR and hypothalamic–pituitary–adrenal responses to stress [63]. These researchers subsequently showed that differences in maternal care modify the expression of more than 900 genes in the offspring. The probable involvement of epigenetic reprogramming in these effects was strongly implied by the observation that a proportion of these changes could be modified by treatment with a HDAC inhibitor or with the methyl donor methionine [64]. Thus an epigenetic determinant of maternal behavior may be transmitted across generations.

2.4. Vernalization in plants

In addition to mammals, the contributions of environmental and epigenetic factors have also been studied in the plants. One of the best examples of environmental effects influencing the physiology of an organism by modifying its epigenetic status is the phenomenon of vernalization, in which exposure of a plant to low temperatures induces earlier flowering [65]. A protein encoded by *flowering locus C* (*FLC*), which acts as a repressor of flowering in Arabidopsis was identified [66]. Exposure to low-temperatures down-regulates *FLC* activity and induces earlier flowering, but interestingly *FLC* activity together with late flowering are restored in each plant generation. The suppression of *FLC* is associated with a reduction of histone H3 trimethyl-lysine 4 (H3K4), and acetylation of both histones H3 and H4, around the promoter-translation start of *FLC*.

2.5. Other nutritional factors and their effect on epigenetics

Nutrition is a major environmental aspect that may influence epigenetic mechanisms in multitude of ways. A number of biologically active food constituents have been shown to affect the metabolic processes associated with energy metabolism through changes in DNA methylation status of genes directly or indirectly. In obese individuals, excess adipose tissue accumulates over time as a consequence of energy intake exceeding expenditure. Adipocytes are a rich source of endocrine factors and other pro-inflammatory cytokines (such as TNF-α and IL-6). These pro-inflammatory cytokines are notorious for their adverse effects in causing increased inflammation, which is strongly associated with carcinogenesis [67]. Indeed, inflammatory bowel disease has been shown to be a driver of aberrant DNA methylation in the colon [12,68]. One potential mechanism for this effect is through the activity of IL-6, which has been shown to support the aberrant methylation of the *p53* promoter via up-regulation of DNMT1 gene expression [69,70].

3. Epigenetic therapy

Epigenetic therapy, the use of drugs to correct epigenetic defects, is currently a new and fascinating area for drug development in the field of cancer prevention and therapy. Epigenetic therapy is a potentially very useful form of therapy because epigenetic defects, in contrast to genetic defects, are reversible [71,72]. Besides their promise as therapeutic agents, epigenetic drugs may also be used for prevention of various diseases, including cancer chemoprevention [73]. Additionally, there is growing enthusiasm that epigenetic drugs alone or in combination with conventional anticancer drugs may prove to be a significant advance over the conventional anticancer drugs, which inherently tend to be very toxic by themselves [74]. Given the fact that epigenetic alterations underpin a broad range of human diseases, the scope of epigenetic therapy is tremendous and likely to expand in the coming years.

The current generation of epigenetic drugs primarily target to inhibit the activity and expression of DNMTs and HDACs. However, since many other molecules are also involved in epigenetic mechanisms that regulate gene expression, there are other potential targets, which yet remain undiscovered. Nonetheless, epigenetic drugs presently under evaluation in various pre-clinical and clinical trials can be classified into two groups, depending on whether they inhibit DNMTs or HDACs. Among the DNMT inhibitors, nucleoside inhibitors, such as 5-azacytidine (5-Aza-CR, or commercially available as Vidaza) and 5-aza-2-deoxycytidine (5-Aza-CdR, or commercially sold as Decitabine) are the most important and widely studied epigenetic drugs [75]. In addition to this, certain non-nucleoside inhibitors such as procainamide, procaine and EGCG have also shown certain potential for inhibiting DNMT activity in various experimental and clinical studies [76–81]. With regards to HDAC inhibitors, trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA), valproic acid and phenyl butyrate, have been widely used with some success in various studies [82–85]. Several of these potentially useful epigenetic drugs are undergoing preclinical and clinical drug trials. Most of these trials have involved various types of cancers such as solid tumors and hematological malignancies [73,86].

Although the current generation of epigenetic drugs have provided the proof of principle in its favor, epigenetic therapy has its limitations. Some of these shortcomings include that both DNMT and HDAC inhibitors may activate oncogenes due to lack of specificity, resulting in accelerated tumor progression [87]. Moreover, epigenetic states, once corrected, may revert to the original state because of the reversible nature of DNA methylation patterns [88]. Taken together, the lack of specificity and the associated high levels of toxicity profiles with the synthetic epigenetic drugs have prompted the dire need for the discovery and development of safe and more specific epigenetic chemopreventive and therapeutic drugs that can translate into clinics in the near future. Epidemiological and experimental data in recent years have clearly provided evidence that diet and diet-derived plant polyphenols have potent anti-cancer properties, and some of these effects are orchestrated via modulation of epigenetic machinery within cancer cells.

4. Dietary polyphenols and cancer chemoprevention

Polyphenols constitute one of the largest and ubiquitous group of phytochemicals. One of the primary functions of these plant-derived polyphenols is to protect plants from photosynthetic stress, reactive oxygen species, and consumption by herbivores. Polyphenols are also an essential part of the human diet, with flavonoids and phenolic acids being the most common ones in food. Not surprisingly, there is a growing realization that lower incidence of cancer in certain populations may probably be due to consumption of certain nutrients, and especially polyphenol rich diets. Consequently, a systematic dissection of the chemopreventive potential of polyphenolic compounds in the recent years has clearly supported their health benefits, including anti-cancer properties. Given the challenges of cancer therapy, 'chemoprevention'-which uses pharmacological or natural agents to impede, arrest or reverse carcinogenesis at its earliest stages' remains the most practical and promising approach for the management of cancer patients [89].

Till date, a substantial number of studies in cultured cells, animal models and human clinical trials have illustrated a protective role of dietary polyphenols against different types of cancers [90–93]. Polyphenols are present in fruits, vegetables, and other dietary botanicals and some of these are depicted in Fig. 2. Some estimates suggest that more than 8000 different dietary polyphenols exist, and these can be divided into ten different general classes based on their chemical structure [94]. Phenolic acids, flavonoids, stilbenes and lignans are the most abundantly occurring polyphenols that are also an integral part of everyday nutrition in populations worldwide. Some of the common examples of the most studied and promising cancer chemopreventive polyphenols include EGCG (from green tea), curcumin (from curry) and resveratrol (from grapes and berries). Significant gains have been made in understanding the molecular mechanisms underpinning the chemopreventive effects of polyphenols, and consequently, a wide range of mechanisms and gene targets have been identified for individual compounds. Various mechanistic explanations for their chemopreventive efficacy include their

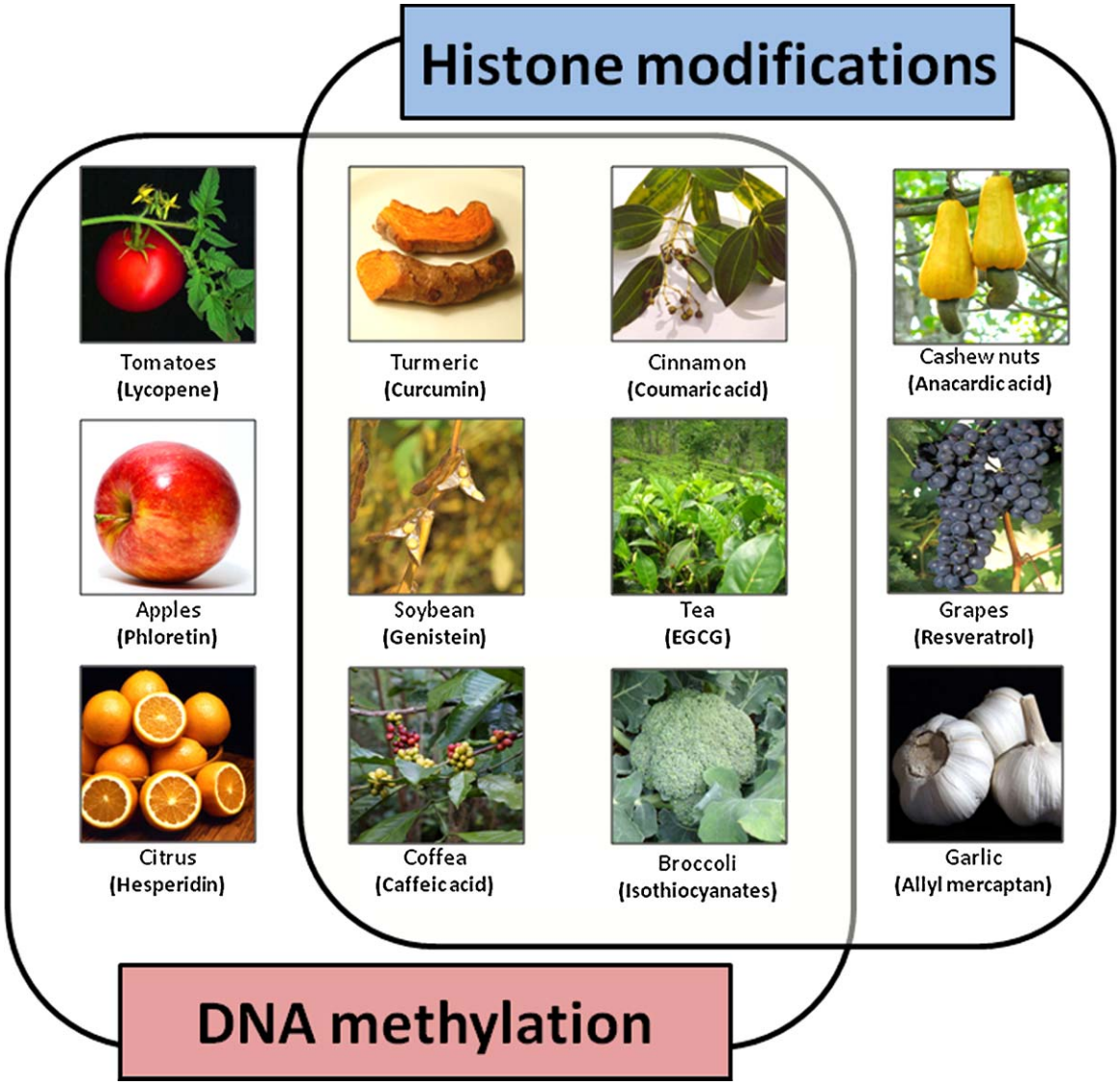

Fig. 2. Illustration depicting major plants with evidence for epigenetic modifications. The figure illustrates photographs from major plants with demonstrated evidence for epigenetic alterations in cancer cells. The 'active principles' for each of the plants are shown within parenthesis. These images were borrowed from various websites for illustration purposes only, and these websites are listed in Supplementary Table 1.

ability to interrupt or reverse the carcinogenesis process by acting on intracellular signaling network molecules involved in the initiation and/or promotion of cancer, or their potential to arrest or reverse the progression stage of cancer [95,96]. Polyphenolic compounds may also trigger apoptosis in cancer cells through the modulation of a number of key elements in cellular signal transduction pathways linked to apoptosis (caspases, *bcl-2* genes) [90,95,96]. Several elegant reviews have described in detail specific genetic and signaling mechanisms that are targeted by different polyphenols, and this is beyond the scope of this review article [97–99]. However, recent research has suggested that some of the chemopreventive potential of dietary polyphenols may in part be due to their ability to modulate epigenetic alterations in cancer cells. This is of interest, as epigenetic modifications occur early and are potentially reversible, making dietary polyphenol-induced chemoprevention of various human cancers an attractive possibility from a clinical standpoint. However, the mechanism how flavonoids do regulate and effect various epigenetic modifications in cancer cells is a topic that is still in its infancy. Nevertheless, increasing number of reports have repeatedly shown the promise of epigenetic prevention and possibly therapy by dietary polyphenols. This review, which is first of its kind, provides a comprehensive review of the chemopreventive effects of various dietary polyphenols in regulating specific epigenetic alterations in human cancers. In particular, in the following sections of this review, we will summarize the existing data on the role of a large number of dietary agents on DNA methylation, histone modifications and regulation of expression of non-coding miRNAs in various *in vitro* and *in vivo* models of human cancers.

5. Polyphenols and DNA methylation

As mentioned earlier, hypermethylation induced transcriptional silencing of tumor suppressor genes constitutes a frequent epigenetic defect in many human cancers. Reversal of gene hypermethylation, which may in part be achieved by inhibiting DNMT activity in cancer cells, is a plausible and promising avenue for developing epigenetic drugs. In this regard, in spite of the promising effects shown by synthetic DNMT inhibitors in clinical studies, their usefulness has been limited due to lack of specificity and resultant toxicity. Several dietary polyphenols have shown potential as DNMT inhibitors and in their ability to reverse

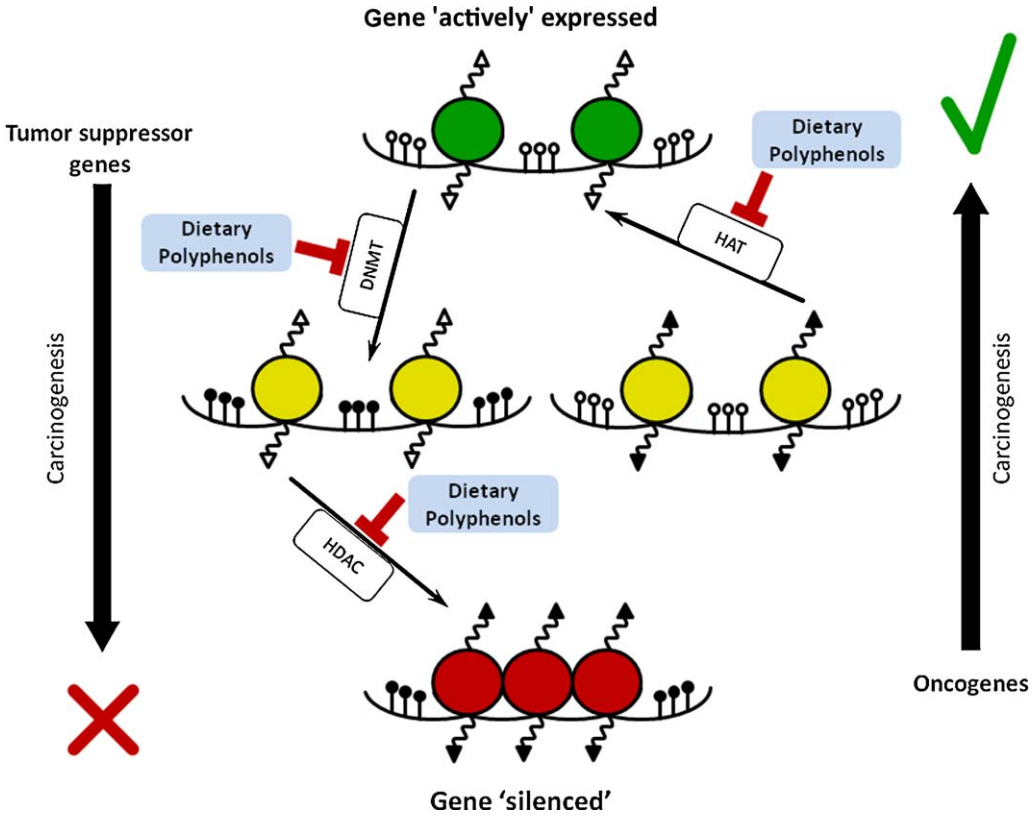

Fig. 3. Effects of dietary polyphenols on the DNA methylation and histone modifications. Simplified scheme demonstrates a number of epigenetic changes that occur during carcinogenesis. In cancers, tumor suppressor genes become "inactivated" (shown as red circles) while oncogenes are "activated" (green circles). Epigenetic gene expression regulation is a complex process and several key enzymes play crucial roles. DNA methyltransferase (DNMT) is responsible for transfer of methyl group to 5′-cytosine. Histone acetylases (HAT) and histone deacetylases (HDAC) are responsible for the acetylation and de-acetylation of lysine residues within histone tails, respectively. Because of these histone modifications, conformational changes in chromatin structure lead to changes in DNA accessibility for transcription regulators and polymerases. Polyphenols can impact these enzymes in specific ways induces reversibility of epigenetic dysregulation in cancer cells.

methylation-induced silencing and restore the expression of various tumor suppressor genes (Fig. 3). Herein, we have summarized in detail, experimental data demonstrating the effect of various dietary polyphenols on DNA methylation changes in various models of human cancers (Table 1).

5.1. Epigallocatechin-3-gallate (EGCG)

EGCG, the major polyphenol in green tea, has been extensively studied as a potential demethylating agent. EGCG is methylated by catechol-O-methyltransferase (COMT), the enzyme responsible of the inactivation of catechol molecules, such as dietary polyphenols. This enzyme introduces a methyl group to the catecholamine group, which is donated by S-adenosyl methionine (SAM). Demethylation of SAM results in the formation of S-adenosyl-L-homocysteine (SAH), and as SAH is a potent inhibitor of DNMT. Generation of SAH has been hypothesized as one of the mechanisms for the demethylating properties of this compound. On the other hand, EGCG can form hydrogen bonds with different residues in the catalytic pocket of DNMT, thus acting as a direct inhibitor of DNMT1 [100,101]. The inhibition of DNMT may prevent the methylation of the newly synthesized DNA strand, resulting in the reversal of the hypermethylation and the re-expression of the silenced genes. Finally, it has been shown that EGCG is also an efficient inhibitor of human dihydrofolate reductase. Like other antifolate compounds, EGCG acts through interaction with folic acid metabolism in cells, causing the inhibition of DNA and RNA synthesis and altering DNA methylation [102].

In a seminal paper in 2003, Fang et al. showed that treatment of human esophageal cancer cells with EGCG caused a concentration- and time-dependent reversal of hypermethylation of several known tumor suppressor genes such as *p16*, *RAR*, *MGMT*, and *MLH1* genes [103]. In the same work, reactivation of some methylation-silenced genes by EGCG was also demonstrated in human colon cancers and prostate cancer cells. Since then, several groups found similar *in vitro* results. Partial demethylation of hypermethylated *RARβ* by EGCG was demonstrated in breast cancer cell lines MCF-7 and MDA-MB-231 cells. Kato et al. showed that treatment of oral cancer cells with EGCG partially reversed the hypermethylation status of the *RECK* gene and significantly enhanced the expression level of *RECK* mRNA [104]. Pandey et al. demonstrated that exposure of human prostate cancer LNCaP cells to green tea polyphenols caused a concentration- and time-dependent re-expression of a known precursor to the genesis of prostate cancer (*GSTP1*), and methylation analysis revealed extensive demethylation in the *GSTP1* promoter region [105]. Berletch et al. showed that treatment of MCF-7 breast cancer cells with EGCG resulted in a time-dependent decrease in *hTERT* promoter methylation [80,106,107].

On the other hand, significant demethylation and activation of several genes by EGCG were not observed by other authors. Chuang et al. examined a total of six different genes/repetitive elements (*p16*, *RARβ*, *MAGE-A1*, *MAGE-B2* and *Alu*) in three separate cell lines (T24, HT29, and PC3) for their DNA methylation levels and their mRNA expression levels using several demethylating agents [108]. Treatment with EGCG did induce neither DNA demethylation nor reexpression of the analyzed genes. In addition, Stresemann et al. also performed a comparative analysis of compounds that had been previously reported to inhibit DNA methyltransferase activity in cancer cell lines, including EGCG [109]. These authors

Table 1
Polyphenols and DNA methylation.

Dietary agent	Plant source	Molecular mechanism	Validated gene target(s)	*In vitro* model	*In vivo* model	Concentration	Treatment duration	References
Apigenin	Parsley, celery	DNMT inhibitor		Esophageal		20–50 μM	*	[103]
Baicalein	Indian Trumpet	DNMT inhibitor		Breast		20–40 μM	3 days	[132]
Betanin	Beetroot red	DNMT inhibitor		Breast		20–40 μM	3 days	[132]
Biochanin A	Soy	DNMT inhibitor		Esophageal; Prostate	Daphnids	20–100 μM	6 days	[103,115,230]
Caffeic acid	Coffea	DNMT inhibitor	*RARβ, CDKN2A*	Breast		1–50 μM	8 days	[126]
Catechin	Green tea	DNMT inhibitor	*RARβ*	Breast		5–50 μM	3–6 days	[101]
Chlorogenic acid	Coffea	DNMT inhibitor	*RARβ, CDKN2A*	Breast		1–50 μM	8 days	[126]
Coumaric/ Hydroxycinnamic acid	Cinnamon	DNMT inhibitor		Esophageal		20–50 μM	*	[103]
Curcumin	Turmeric	DNMT inhibitor		Esophageal; Leukemia;		3–50 μM	3 days	[103,130,131]
Cyanidin	Berries, grapes	DNMT inhibitor		Breast		20–40 μM	3 days	[132]
Daidzein	Soy	DNMT inhibitor		Esophageal; Prostate; Mice		20–100 μM	6 days	[103,115,121]
Ellagic Acids	Berries	DNMT inhibitor		Breast		20–40 μM	3 days	[132]
Epicatechin	Green tea	DNMT inhibitor		Esophageal; Breast		50 μM	*	[100,101]
Epicatechin gallate	Green tea	DNMT inhibitor		Esophageal		20–50 μM	*	[100]
Epigallocatechin	Green tea	DNMT inhibitor		Esophageal		20–50 μM	*	[100]
Epigalocatechin-3-gallate	Green tea	DNMT inhibitor	*RARβ, MGMT, MLH1, CDKN2A, RECK, TERT, RXRα, CDX2, GSTP1, WIF1*	Esophageal; Oral; Prostate; Urinary; Lung; Colon; Leukemia; Lymphoma;	Agouti mouse Mouse models: skin, prostate, colon and uterine cancer Human: gastric and oral cancers, premenopausal women	10 μg/ml; 20–100 μM; 0.3–0.6%	2–6 days	[78,80,100–105, 108–111,113,114, 114,192,231]
Fisetin	Poison ivy	DNMT inhibitor		Esophageal; Breast		5–20 μM		[101,103]
Galangin	Galangal root, propolis	DNMT inhibitor		Breast		20 μM	3 days	[132]
Garcinol	Garcinia	DNMT inhibitor		Esophageal		20–50 μM	*	[103]
Genistein	Soy	DNMT inhibitor ↓ DNMTs, MBD1, MBD4 MeCP2 expression	*RARβ, MGMT, CDKN2A, GSTP1, HMGN5, BTG3, TERT*	Esophageal; Prostate	Daphnids	3.75–100 μM; 50–300 mg/kg/d	3–6 days	[7,8,103,115–123, 192,230,232]
Hesperidin	Citrus	DNMT inhibitor		Esophageal		20–50 μM	*	[103]
Isothiocyanates	Broccoli, broccoli sprouts	Unknown	*GSTP1*	Esophageal; Prostate		2.5 μM	5 days	[128,129]
Luteolin	Parsley, celery	DNMT inhibitor		Esophageal		20–50 μM	*	[103]
Lycopene	Tomatoes	Unknown	*GSTP1, RARβ, HIN-1*	Breast		2 μM	1–2 weeks	[117]
Myricetin	Berries	DNMT inhibitor		Esophageal; Breast		5–25 μM	3 days	[101,103,132]
Naringenin	Citrus	DNMT inhibitor		Esophageal		20–50 μM	*	[103]
Phloretin	Apples	DNMT inhibitor		Breast		20–40 μM	3 days	[132]
Piceatannol (Resveratrol metabolite)	Grapes, blueberries	DNMT inhibitor		Breast		20–40 μM	3 days	[132]
Protocatechuric acid	Olives	DNMT inhibitor		Breast		20–40 μM	3 days	[132]

Quercetin	Citrus	DNMT inhibitor	*CDKN2A*	Esophageal; Breast; Colon	5–20 μM	5 days	[101,103,233]
Resveratrol	Grapes, wines, eucalyptus	DNMT inhibitor		Breast; Lung	20–40 μM	1 day	[132,133]
Rosmarinic acid/Rosmarinic	Rosemary	DNMT inhibitor		Breast	20–40 μM	3 days	[132]
Sinapic acid	Sinapis (mustard)	DNMT inhibitor		Breast	20–40 μM	3 days	[132]
Sulforaphane	Broccoli	↓ DNMTs expression		Esophageal; Colon	50 μM	*	[127,192]
Syringic acid	Red grapes	DNMT inhibitor		Breast	20–40 μM	3 days	[132]

* DNA methyltransferase activity assay using only nuclear extracts.

determined the cytosine methylation level and the methylation status of *TIMP3* in different cell lines and found that EGCG did not inhibit DNA methylation. There are many potential reasons for the discrepancies between studies, including different methods of analysis, possible gene-specificity or cell line–specificity of EGCG, or that treatment method might had been ineffective to show efficacy. Based on their results, Stresemann et al. argued that cellular effects induced by EGCG could probably be attributed to the oxidative stress induced by this compound.

Whether EGCG can reverse DNA hypermethylation and reactivate methylation-silenced genes *in vivo* still remain to be determined. Mittal et al. showed that topical treatment of EGCG in hydrophilic cream inhibits UVB induced global DNA hypomethylation pattern in chronically UVB-exposed mice [110]. Immunohistochemical detection of DNA methylation pattern was performed using anti-5-methylcytosine monoclonal antibody. Since global DNA hypomethylation is a phenomenon usually associated with hypermethylation and inactivation of specific genes during carcinogenesis, the authors hypothesized that their observation was not contradictory to the concept that EGCG can prevent or reverse the hypermethylation of certain specific genes. Kinney et al. recently tested whether oral consumption of green tea polyphenols (GTP) could affect normal or cancer-specific DNA methylation *in vivo*, using a mice model [111]. Wild-type and transgenic adenocarcinoma of mouse prostate (TRAMP) mice were given 0.3% GTPs in drinking water beginning at 4 weeks of age. To monitor DNA methylation, the authors measured 5-methyldeoxycytidine (5mdC) levels, methylation of the B1 repetitive element, and methylation of the *Mage-a8* gene. GTP treatment did not inhibit tumor progression in TRAMP mice and no dose-dependent alterations in DNA methylation status were observed. Yuasa et al. performed a retrospective analysis examining the methylation status of several genes in primary gastric carcinomas in relation to past lifestyle of the patients, including dietary habits [112,113]. Methylation of *CDX2* and *BMP-2*, measured by methylation specific PCR, correlated with the decreased intake of green tea and cruciferous vegetables.

Finally, Tsao et al. recently published a phase II randomized, placebo-controlled trial of green tea extract (GTE) in patients with high-risk oral premalignant lesions (OPL) [114]. The OPL clinical response rate was higher in all GTE arms at different doses ($n = 28$; 50%) versus placebo ($n = 11$; 18.2%; $P = 0.09$) but did not reach statistical significance. Only two patients in the GTE arm had baseline *p16* promoter methylation that could be evaluated following treatment, which did not reverse methylation status in either patient.

Although most of the evidence about the epigenetic properties of tea natural compounds has focused on EGCG, also other catechins such as catechin, epicatechin, epicatechin gallate and apigallocatechin have also been found to share similar features, although with much less DNMT inhibitory activity compared to EGCG [100,101,103].

5.2. Genistein

Genistein, one of the many phytoestrogens contained in soybeans, has been lately studied as a demethylating agent. Stronger than other soy isoflavones (Biochanin A or diadzein), genistein induces a dose-dependent inhibition of the DNMT activity, showing competitive and noncompetitive inhibition with respect to the substrate poly(dI-dC).poly(dI-dC) and noncompetitive inhibition with respect to SAM [115,116].

Treatment of KYSE 510 esophageal squamous cell carcinoma cells with genistein partially reversed DNA hypermethylation and reactivated *p16*, *RARβ* and *MGMT*. This was demonstrated by the appearance of unmethylation-specific bands by methylation-

specific-PCR as well as by the increased mRNA levels determined by RT-PCR. Partial reversal of DNA hypermethylation and reactivation of *RAR*β were also observed in KYSE 150 cells and prostate cancer LNCaP and PC3 cells. In the same work, genistein in combination with other DNA methyltransferase or HDAC inhibitors (such as TSA) enhanced the reactivation of methylation-silenced genes [115].

King-Batoon et al. found that a low, nontoxic concentration of genistein (3.125 μM) partially demethylated the promoter of the *GSTP1* tumor suppressor gene in MDA-MB-468 breast cancer cells [117]. RT-PCR confirmed a lack of *GSTP1* expression in untreated MDA-MB-468, with restoration of *GSTP1* expression after genistein treatment. Similarly, treatment of renal and prostate cancer cells with genistein induced reversal of hypermethylation and reactivation of B-cell translocation gene 3 (*BTG3*), a known tumor suppressor gene in some malignancies [118,119].

Although *in vitro* studies have shown that genistein apparently induces DNA demethylation through DNMT inhibition, three animal studies have observed rather increased DNA methylation following the treatment. Day et al. treated male mice with different diet schemes including genistein for 2–4 weeks and control diet, and analyzed methylation changes in different tissues using a technique called mouse differential methylation hybridization (DMH) array [120]. In this assay, the presence or absence of a spot would indicate hypermethylation or hypomethylation, respectively, relative to the control, including 300 spots covering 900 CpG islands. Interestingly, DNA from prostate showed a particular spot on the 4-week genistein treatment membrane significantly darker than the equivalent spots on any other membrane, thus suggesting hypermethylation caused by genistein. Dolinoy et al. analyzed the effect of genistein exposure during gestation on DNA methylation in the offspring, due to the fact that this is when the epigenome is most susceptible to environmentally induced dysregulation [7]. To determine if maternal genistein affects offspring by altering the epigenome *in utero*, the authors assessed coat color, DNA methylation, and body weight in genetically identical heterozygous yellow agouti (*Avy*/*a*) offspring. The expression of the *Avy* allele usually leads to yellow fur, obesity and tumorigenesis, while CpG methylation in an intracisternal A particle retrotransposon upstream of the *Agouti* gene correlates inversely with ectopic *Agouti* expression. The results showed that genistein induced CpG hypermethylation of six CpG sites in this region, shifting coat-color distribution toward pseudoagouti (brown), thereby decreasing the incidence of adult-onset obesity in *Avy*/*a* offspring. Guerrero-Bosagna et al. evaluated the sexual maturity, morphometric parameters and DNA methylation status in mice treated with soy isoflavones (genistein and daidzein) and found that this diet can result in an advancement of sexual maturation in female pups as well suppress normal gender differences in the DNA methylation pattern of a tissue specific methylated gene such as *Acta1*, inducing hypermethylation of this gene only in females [121]. Conversely, Tang et al. showed that treatment of neonatal mice with genistein prevented the hypermethylation of *nucleosomal binding protein* 1 (*Nsbp*1) in the uterus throughout life, inducing uterine adenocarcinoma in aging animals [122].

The effect of genistein on methylation in humans has been recently tested. Qin et al. performed a double-blind, randomized trial in 34 healthy premenopausal women receiving 40 mg or 140 mg isoflavones daily (including genistein, daidzein, and glycitein) through one menstrual cycle [123]. Methylation assessment of 5 cancer related genes known to be methylated in breast cancer (*p16*, *RASSF1A*, *RARβ2*, *ER*, and *CCND2*) was performed on intraductal specimens. In agreement with the animal data, the results showed that *RARβ2* and *CCND2* hypermethylation was increased after treatment and correlated with the genistein level.

5.3. Lycopene

Lycopene is a bright red carotene and carotenoid pigment found in tomatoes and other red fruits and vegetables. Lycopene can modulate the expression of numerous genes relevant to cell cycle control, DNA repair, and apoptosis in breast cancer cells as shown in gene array studies [124,125]. King-Batton et al. showed that treatment of MDA-MB-468 breast cancer cells with a single dose of lycopene partially demethylated the promoter of the *GSTP1* tumor suppressor gene, with a concomitant increase in expression [117].

5.4. Coffee polyphenols

Caffeic acid and chlorogenic acid are catechol-containing coffee polyphenols that, in a similar way to the tea polyphenols, have shown to be demethylating agents. Lee et al. studied the modulating effects of these two compounds on the *in vitro* methylation of synthetic DNA substrates and also on the methylation status of the promoter region of *RARβ* in two human breast cancer cells lines [126]. The presence of caffeic acid or chlorogenic acid inhibited in a concentration-dependent manner the DNA methylation catalyzed by DNMT1, predominantly through a non-competitive mechanism. This inhibition, similar to other dietary polyphenols, was largely due to the increased formation of SAH. Treatment of MCF-7 and MAD-MB-231 human breast cancer cells with these two compounds partially inhibited the methylation of the promoter region of *RARβ*.

5.5. Sulforaphane

Sulforaphane, a dietary phytochemical obtained from broccoli, has been implicated in several physiological processes consistent with anticarcinogenic activity, including enhanced xenobiotic metabolism, cell cycle arrest, and apoptosis. Although the effect of sulforaphane as a demethylating agent has not been specifically studied, this compound was found to downregulate DNMT1 in CaCo-2 colon cancer cells [127].

5.6. Isothiocyanates

Isothiocyanates comprise another class of dietary compounds known to affect the epigenome. Isothiocyanates are metabolites of glucosinolates present in a wide variety of cruciferous vegetables and demonstrated to have anticancer properties. Treatment of prostate cancer cells with phenethyl isothiocyanate, a metabolite of gluconasturtin from watercress, was shown to lead to demethylation and re-expression of *GSTP1* [128]. On the other hand, treatment with different isothiocyanates prevented the esophageous tumorigenesis induced by the methylating agent *N*-nitrosomethylbenzylamine (NMBA) in male rats [129].

5.7. Curcumin

Curcumin, the major component of tumeric, has shown strong anti-inflammatory, anti-angiogenic and antioxidant, wound healing and anticancer effects for various diseases. It has been recently shown that curcumin and one of its major metabolites, tetrahydrocurcumin can inhibit M.SssI, an DNMT1 analog, activity and its inhibitory activity may arisen from a potential covalent blocking of a catalytic group in DNMT1. This inhibition seems to be lower than other compound such as EGCG [103,130,131]. More interestingly, curcumin exposure to genomic DNA of MV4-11 leukemia cell line induced a decrease in global DNA methylation comparable to decitabine [130]. Our group has recently performed genome-wide methylation analysis in several colon cancer cell lines treated with curcumin, and have discovered that curcumin

Table 2
Polyphenols and histone modifications.

Dietary agent	Plant source	Molecular mechanism	Histones and gene target(s)	*In vitro* model	*In vivo* model	Concentration	References
3,3-diindolylmethane	Broccoli	↓ HDAC expression	*COX-2*	Colon; Breast	Mouse: colon cancer	10–60 μM	[196–198]
6-methoxy-2E,9E-humuladien-8-one	Ginger	HDAC inhibitor		Breast		1.25 μM	[234]
Allicin	Garlic	Unknown	H4 acetylation	Erythroleukemia		2–200 μM	[176]
Allyl mercaptan	Garlic	HDAC inhibitor	H3/H4 acetylation *p21WAF1*	Erythroleukemia; Liver; Colon	Rat: liver	2–500 μM (100mg/kg)	[173–175, 177,178]
Anacardic acid	Cashew nuts	HAT inhibitor	H3K9 and H3K14 deacetylation *NF-kB* activation	Leukemia; Plasmodium; Cervix; Embryonic kidney; Breast; Lymphoma; Prostate; Lung; Esophageal; Skin		3–200 μM	[138,139, 153–160]
Biochanin A	Soy	HDAC inhibitor	*RARβ*	Esophageal; Prostate		20–100 μM	[115]
Butein	Varnish Tree	Induction of SIRT1 activity		Cervix	Drosophila	100 μM	[203,204]
Caffeic acid	Coffea	HDAC inhibitor		Cervix; Colon		1–2.54 mM	[152,235]
Catechin	Green tea	HAT inhibitor		Lymphocytes		100 μM	[165]
Chlorogenic acid	Coffea	HDAC inhibitor		Cervix		0.375 mM	[152]
Cinnamic acid	Cinnamon	HDAC inhibitor		Cervix; Colon		1–2 mM	[152,235]
Coumaric/ Hydroxycinnamic acid	Cinnamon	HDAC inhibitor		Cervix; Colon		1–2 mM	[235]
Curcumin	Turmeric	HAT and HDAC inhibitor	H3/H4 deacetylation *GATA4, EOMES, GZMB, PRF1*	Cervix; HIV; Hepatoma; Leukemia; Prostate; Brain; Lymphoma; Lymphocytes;	Plasmodium falciparum; Herpes virus Mouse: epilepsy Rat: diabetes, heart failure	6.25–135 μM (0.3–75 mg/kg)	[134–152]
Daidzein	Soy	HDAC inhibitor	Histones acetylation *RARβ*	Esophageal; Prostate		12.8–100 μM	[115,199]
Diallyl disulfide	Garlic	HDAC inhibitor	H3/H4 acetylation *p21WAF*	Erythroleukemia; Leukemia; Liver; Colon; Prostate; Fibroblasts	Rat: colon cancer	20–200 μM, (42–200 mg/kg)	[173,175,177, 179–183,236]
Dihydrocoumarin	Yellow Sweet Clover	SIRT1 and SIRT2 inhibitor	*p53* acetylation	Lymphoblastoid cell line		0.75–50 mM	[220]
Epicatechin	Green tea	HAT inhibitor		Lymphocytes		100 μM	[165]
Epicatechin gallate	Green tea	HAT inhibitor		Lymphocytes		100 μM	[165]
Epigallocatechin	Green tea	HAT inhibitor		Lymphocytes; Colon		100 μM	[165,166]
Epigalocatechin-3-gallate	Green tea	HAT inhibitor	H3/H4 acetylation	Lymphocytes; Colon; Keratinocytes; Prostate		5–100 μM	[105,165–167]
		HMT inhibitor	H3K27 tri-methylation *NF-κB, IL-6, BMI-1, EZH2, SUZ12*				
Equol	Soy	HDAC inhibitor	H2A/H2B/H3/H4 acetylation	Drosophila		12.8 μM	[199]
Fisetin	Poison ivy	SIRT1 activator		Cervix; Drosophila		100 μM	[203,204]
Flavone	Feijoa	HDAC inhibitor	Histones acetylation *p16, p21, TRAIL*	Myeloid leukemia		170–340 μM	[237]
Garcinol	Garcinia	HAT inhibitor	Global gene expression down- regulation	Leukemia; Cervix; Lymphocytes; HIV		5–100 μM	[139,156, 161–164,238]
Genistein	Soy	HAT activator HDAC inhibitor	H2A/H2B/H3/H4 acetylation *p21, p16, PTEN, CCLD, p53, FOXA3, SIRT1, BTG3 hTERT, RARβ*	Esophageal; Prostate; Breast; Renal		5–100 μM	[115,116,118, 119,199–201]

Table 2 (*Continued*)

Dietary agent	Plant source	Molecular mechanism	Histones and gene target(s)	*In vitro* model	*In vivo* model	Concentration	References
Isoliquiritigenin	Liquorice	SIRT1 activator		Cervix; Drosophila		100 μM	[203,204]
Isothiocyanates	Broccoli, wasabi	HDAC inhibitor	H3/H4 acetylation, *p21*, *GSTP1*	Prostate; Erythroleukemia; Leukemia; Prostate		20–100 μM	[128,174, 193–195]
Luteolin	Parsley, celery	SIRT1 activator		Cervix		100 μM	[203]
Piceatannol	Grapes, blueberries	SIRT1 activator		Cervix; Drosophila		100 μM	[203,204]
Polyphenon B	Black and green tea	↑ HDAC1 expression			Rat: liver cancer	0.05%	[168]
Quercetin	Citrus, apple, berries	SIRT1 activator HAT inhibitor	*IP-10, MIP-2*	Cervix; Drosophila; Small intestine;	Mouse: bowel inflammation	100 μM	[203,204,219]
Resveratrol*	Grapes, wine, eucalyptus	SIRT1 activator	*TNFα, IL-8, RBP*	Cervix; Endothelial; Embryonic kidney; Macrophages; Lung; Liver; Cardiomyocytes;	Yeast; Drosophila; Mouse: colon cancer; Rat: lung cancer	10–200 μM	[203–212, 239–242]
S-allylmercaptocysteine	Garlic	HDAC inhibitor	H3/H4 acetylation	Erythroleukemia; Colon		20–250 μM	[176,178]
Sanguinarine	Opium poppy	Histone methylation inhibitor HAT inhibitor	H3K9/H3K4 demethylation H3/H4 deacetylation	Liver; Cervix		5–75 μM	[221]
Silibinin	Milk thistle	↑ histone acetylation	H3/H4 acetylation *p21, p27, CASP3, CASP9.*	Hepatoma		120–240 μM	[243]
Sulforaphane	Broccoli	HDAC inhibitor	H3/H4 acetylation *RARβ, HBD-2, p21,BAX*	Esophageal; Prostate; Colon; Kidney; Breast	Mouse: colon cancer; prostate cancer xenografts Human: blood	15–25 μM (443 μg/kg, 68 g)	[115,166, 185–191]
Theophylline	Black and green tea	HDAC activator		Alveolar macrophages; Epithelial cells; Blood monocytes		10 μM	[169–172]
Ursolic acid	Basil	HDAC inhibitor	Histone acetylation	Leukemia		5–20 μg/ml	[244]

* This table only provides selected publications for resveratrol as a *SIRT1* inhibitor.

induces global methylation alterations in all cell lines in the time-dependent manner (unpublished data).

5.8. Rosmarinic acid

Rosmarinic acid is a natural polyphenol antioxidant carboxylic acid found in many *Lamiaceae* herbs used commonly as culinary herbs such as lemon balm, rosemary, oregano, sage, thyme and peppermint. Rosmarinic acid has been recently shown to be a potent inhibitor of DNMT1 activity in nuclear extracts from MCF7 breast cancer cells and decrease the protein levels of DNMT1. However, this compound was unable to demethylate and reactivate known hypermethylated genes such as *RASSF1A*, *GSTP1* and *HIN-1* in this cell line [132].

5.9. Resveratrol

Resveratrol, a phytoalexin made naturally by several plants, has been produced by chemical synthesis because of its potential anti-cancer, anti-inflammatory, blood-sugar-lowering and other beneficial cardiovascular effects. There is limited evidence about the potential demethylating activity of this compound. Resveratrol has shown to be a weak DNMT activity inhibitor in nuclear extracts from MCF7 cells, and as rosmarinic acid, was unable to reverse the methylation of several tumor suppressor genes [132]. In MCF-7 cells, resveratrol improved the action of adenosine analogues to inhibit methylation and to increase expression of RARβ2, although without significant effect on its own [133].

5.10. Other compounds with effects on DNA methylation

In addition to various dietary polyphenols described above, further compounds exist for which the evidence to modulate DNA methylation is less robust. Several of these additional compounds are not described here, but are listed in the Table 1.

6. Polyphenols induced histone modifications

In addition to their ability to induced changes in DNA methylation, evidence indicates that dietary polyphenols can also regulate gene expression through changes in histone modifications (Fig. 3). In this regard, several polyphenols are known to possess potent HAT and HDAC inhibitory activities. The text below and Table 2 systematically summarize the current understanding on the effects of dietary polyphenols on histone modifications, which may play a significant role in the chemopreventive potential of these compounds.

6.1. Curcumin

Strong evidence from *in vitro* and *in vivo* experiments suggests that curcumin functions as a potent histone modifying compound, especially as a HAT inhibitor. In one of the earliest studies using computational screening algorithms, curcumin was shown to bind to HAT enzymes in a covalent manner [134,135]. Subsequently, several independent research groups showed that curcumin strongly inhibits p300/CBP activity in cell extracts from multiple cancers including cervix, hepatoma and leukemia at a concentration of 20 μM or higher [136–139]. Using prostate PC3-M cells and peripheral blood lymphocytes, Marcu et al. showed that curcumin selectively promotes proteasome-dependent degradation of p300/CBP without affecting other HATs such as PCAF or GCN5 [135]. Inhibition of p300/CBP was shown to be associated with repression of histones H3/H4 and non-histone proteins such as p53, HIV-Tat protein, as well as HAT-dependent chromatin transcription [136]. Moreover, curcumin was shown to effectively prevent histone hyperacetylation induced by the histone deacetylase (HDAC) inhibitor MS-275 in both cancer cells (PC3-M and HeLa) and peripheral blood lymphocytes [135,140].

In addition to its effect in cancer cells, curcumin has further been shown to modulate the immunologic memory of CD8+ T-lymphocytes partially through deacetylation of H3K9 at the promoter region of several key transcription factors such as *Eomesodermin* (*EOMES*) and its targets *perforin* (*PRF*) and *granzyme B* (*GZMB*) [141]. In brain cancer cells and brain-derived neural cells, curcumin effectively induced histone H3/H4 hypoacetylation, and this effect was associated with neuronal differentiation, synaptogenesis, progenitor cell migration and neurogenesis both *in vitro* and *in vivo*, suggesting its importance in neural stem cell fate controlling [142]. Besides human cells, Cui et al. showed that curcumin strongly inhibits one of the *Plasmodium falciparum* HAT's nuclear activity (*P. falciparum general control nonderepressed 5* (*PfGCN5*)) which induced hypoacetylation of H3K9 and -K14 [143]. The same group further demonstrated that curcumin-related H3K9 hypoacetylation at the promoter region of the certain genes was associated with gene silencing [144].

Building upon the evidence gathered from *in vitro* studies, several groups have corroborated the HAT inhibitory effect of curcumin in animal models. In the kainate-induced status epilepticus mice model, that associates with H3S10 phosphorylation, H4 acetylation and CBP activation, pretreatment with curcumin (30 mg/kg) attenuated all histone modifications and the severity of the status epilepticus [145]. Several studies have shown the beneficial effects of curcumin on the progression of streptozotocin-induced diabetes nephropathy in male Sprague-Dawley rats. In this animal model, curcumin treatment was associated with inhibition of p300, NF-κB, H3S10 phosphorylation and H3 hyperacetylation [146,147]. Furthermore, two independent groups have shown that curcumin acts as a protective agent against cardiac hypertrophy, inflammation and fibrosis in animal models through both suppression of HAT activity (p300) and downregulation of *GATA4*, *NF-κB* and *TGFβ/Smad* signaling pathways [148,149]. In these studies, curcumin abrogated H3/H4 acetylation, *GATA4* acetylation levels and relative levels of p300/GATA4 complex, which is otherwise markedly increased in the hypertensive hearts of these rats [148,149].

In addition to HAT-inhibitory effect of curcumin, a few recent studies have inconclusively suggested a possible HDAC-inhibitory effect as well [137]. Using Burkitt-lymphoma Raji cells, Liu et al. and Chen et al. showed that curcumin treatment was associated with down-regulation of HDAC1, HDAC3 and HDAC8 proteins, whereas H4 protein expression was up-regulated [150,151]. Although these results require further experimental confirmation, another recent study has supported the HDAC-inhibitory effects of curcumin [152].

6.2. Anacardic acid

Anacardic acid (AA) is an active compound of cashew nuts that has been shown to be a specific HAT inhibitor. AA has been shown to be a potent inhibitor of p300, PCAF and Tip60 HAT factors [153,154]. Although AA does not affect DNA transcription directly, HAT-dependent transcription was strongly inhibited and was associated with simultaneous histone H3 and/or H4 hypoacetylation in HeLa and MCF7 cancer cells [153,155]. In fact, on the basis of knowledge gained from its HAT inhibitory activity, AA chemical formula has been widely used for the development of new synthetic HAT inhibitors and activators [138,139,153,155–157].

Only very few studies have evaluated the molecular biological relevance of AA-related HAT inhibitory activity. Sung et al. showed that AA inhibits both inducible and constitutive NF-κB activation, and suppresses activation of IκBα kinase which leads to abrogation

of its phosphorylation and eventual degradation in multiple cancer cells (myeloid and T-cell lymphoma cells, human embryonic cells, lung, prostate and esophageal cancer cells) [158]. In the same study, it was demonstrated that AA inhibits acetylation and nuclear translocation of p65, and suppresses NF-κB-dependent reporter gene expression, which is dependent upon p300 HAT expression/activity [158]. In addition, using human dermal fibroblasts Kim et al. demonstrated that AA effectively inhibits UV-induced cancer formation and premature skin aging by inhibiting UV-enhanced levels of *c-H2AX*, *p53*, and acetylation of H3 [159]. In *P. falciparum*, similar to curcumin, AA has also been shown to inhibit PfGCN5 activity in nuclear extracts [160]. In this elegant study, treatment with AA induced hypoacetylation of H3K9 and -K14, and resulted in down-regulation of 207 genes that were partially enriched for H3K9 acetylation. These data provide support for the HAT-inhibitory effects of AA not only in mammalian cells, but also in malaria parasites as well [160].

6.3. Garcinol

Garcinol is a highly cytotoxic polyisoprenylated benzophenone derivative from garcinia fruit rinds. Multiple studies have shown that garcinol is a potent inhibitor of different HATs, such as, p300 and PCAF [139,156,161]. A recent mechanistic work using fluorescence, docking and mutational studies, has revealed that garcinol induces alteration in the secondary structure of the HAT proteins [162]. Analogous to curcumin and AA, garcinol also possesses significant histone H3 and H4 deacetylating activities [161,163]. In addition, garcinol also has the ability to inhibit autoacetylation of p300, which is one of the key regulatory mechanism for its catalytic activity in HeLa cor histones [163]. Although none of the studies have specifically evaluated the effects of garcinol on gene-specific histone modifications, existing data indicates that garcinol and/or its synthetic derivate LTK14, down-regulates the expression of multiple genes in cervical cancer cells and T-lymphocytes, supporting its HAT inhibitory activity [161,164].

6.4. EGCG and green tea polyphenols

EGCG is one of the first compounds that was recognized as an epigenetic modulator in cultured cancer cells. Although effects of EGCG have mainly been studied in the context of DNA methylation, recent data suggest that EGCG also acts as a histone modifier. Of all the catechins present in green tea, EGCG has shown to be is the most promising and potent modulator of histone marks in cancer cells [165]. In a recent study by Choi et al., several green tea polyphenols were screened for their HAT activity in various cell extracts from B-lymphocytes. The authors discovered that among the studied tea polyphenols, EGCG was the most potent HAT inhibitor, and possessed global specificity towards various HAT enzymes in the following order p300 > CBP > Tip60 > PCAF [165]. EGCG treatment inhibited the acetylation of p65 and the expression of NF-κB target genes in response to diverse stimuli, thus having great potential as a chemopreventive agent of chronic inflammation [165]. The activity of EGCG toward other histone modifying enzymes such as HDACs, SIRTs and HMTs remains controversial. While Choi et al. and Nair et al. found no activity toward these enzymes [165,166], Pandey et al. demonstrated that green tea polyphenols show both inhibition of HDAC activity and reduction in mRNA expression of HDAC1, 2 and 3 in prostate cancer cells. These changes were subsequently associated with time-dependent increase in the acetylation of H3 and H4 [105].

In addition to the effect on HAT and HDAC activities, EGCG has recently shown to affect Polycomb Group (PcG) protein complexes PRC2 (EED) and PRC1 (BMI-1) in immortalized keratinocytes and skin cancer cells [167]. Both PRC1 and PRC2 actively participate in epigenetic regulation of gene expression by increasing histone methylation and reducing acetylation, which leads to chromatin compaction and transcriptional silencing of genes in cancer cells [167]. Treatment of skin cancer cells or immortalized keratinocytes with 60 μM EGCG reduced the expression of BMI-1 and EZH2, which was associated with reduction in survival and global reduction in histone H3K27me3, a hallmark of PRC2 complex action [167].

6.5. Other tea polyphenols: polyphenon B and theophylline

There is limited evidence regarding the epigenetic properties of polyphenon B (black tea polyphenol), in cultures cancer cells. In a single study on DAB-induced liver cancer animal model, polyphenon B (0.05%) induced a significant decrease in HDAC1 expression in male Sprague-Dawley rats, compared to the untreated controls [168].

Theophylline, also known as dimethylxanthine, shows a structural similarity to caffeine and is present in low concentrations in tea. Cosio et al. evaluated the HDAC modulating effect of theophylline in smokers and chronic obstructive pulmonary disease (COPD) patients, a situation known to have decreased HDAC activity [169]. Interestingly, theophylline treatment was associated with down-regulation of the inflammatory response through modulation of HAT, HDAC activity, and NF-κB activation. Following studies from the same group demonstrated that low-doses of theophylline increased HDAC activity in epithelial cells and macrophages, and further reduced IL-8 and TNFα concentrations [170–172]. This mechanism occurred at therapeutic concentrations and independently of its phosphodiesterase inhibition, improving the anti-inflammatory effects of steroids [172].

6.6. Allyl-derivates

Allyl-derivates from garlic were one of the first compounds that were described to have an impact on histone acetylation, suggesting that these compounds may inhibit HDAC enzyme activity in mouse and human leukemia cells DS19 and K562 [173]. Initially it was shown that various allyl-derivates such as allyl mercaptan (AM), diallyl disulfide (DADS), S-allylcysteine(SAC), S-allylmercaptocysteine (SAMC) and allicin induce increased histone acetylation (H3/H4) both in cultured cancer cells such as DS19 and at higher concentrations in liver from rats [173–176]. Among various allyl-derivates and precursors, AM is the most potent HDAC inhibitor in colorectal cancer and leukemic cells [173,177,178]. Using docking simulation model with human HDAC8 protein, Nair et al. have demonstrated that AM interacts with the enzyme active site, and this was accompanied by a rapid accumulation of H3/H4 histones [166]. Similar to other HDAC-inhibitors, AM increased histone H3 acetylation on the *CDKN1A* gene, with a concomitant increase in binding of transcription factor Sp3 and p53 to the promoter region [178]. Although less significant, several studies have shown that DADS treatment in CaCo2 and HT29 colorectal cancer cells also produced increased acetylation of H3 and H4, and up-regulation of *CDKN1A* [177,179–183]. SAMC and DADS treatments were also shown to associate with increased *E-cadherin* expression, however, its relationship concerning HDAC inhibitory effects has not been evaluated [180,184]. In addition to *in vitro* evidence accumulated thus far, animal studies with ally-derivatives have shown that treatment with AM and/or DADS increases acetylation of histones and causes up-regulation of p21 expression in normal liver and hepatoma cells and in rat colonocytes [175,180,181]. Although these findings are very encouraging, there is concern about the high concentrations of allyl-derivatives used in animal studies, which are unlikely to be physiologically achievable in humans if such compounds are considered for clinical intervention [175,180,181].

Considering this, it was proposed that SAMC may be a safer and more effective choice, as it was shown to induce growth arrest in mouse erythroleukemia cells at relatively low concentrations [176]. However, SAMC is inherently a weaker HDAC inhibitor that AM or DADS, as evidence when it was tested in prostate cancer cell lines [184].

6.7. Isothiocyanates (sulforaphane and isothiocyanates derivates)

Isothiocyanates such as phenethyl isothiocyanate (PEITC) and sulforaphane (SFN) are the main compounds found at high levels in broccoli. Until now multiple studies have confirmed the potent HDAC inhibitory activity of isothiocyanates. Using human kidney cells and colorectal cancer cells, Myzak et al. have demonstrated that one of the SFN metabolites (SFN-Cys) acts as a HDAC inhibitor, as predicted by computer modeling [185]. Although Nair et al. failed to demonstrate HDAC inhibitory effect when SFN was combine with EGCG in HT29 colon cancer cells [166], several studies have clearly confirmed the HDAC inhibitory activity of SFN (150-25 μM) in multiple human cancer cell lines (colon, prostate and breast cancer cells) [185–188]. HDAC inhibition in cell lines and animals was associated with increased histone H3/H4 acetylation [185–187,189]. Such effects of SFN were associated with increased H4 acetylation in the *p21* and *Bax* promoters, which resulted in significant up-regulation of both gene and protein expression in prostate cancer cells [185–187,189]. However, Pledgie-Tracy et al. failed to observe any increase in histone acetylation induced by SFN in breast cancer cells [188].

In a mice model, SFN-containing diet is optimal for achieving SFN tissue concentrations in the 3–30 μM range [190]. SFN-enriched diets in these animals were shown to suppress tumor development in APCmin/+ mice via increase in overall H3/H4 histone acetylation, and a concomitant up-regulation of p21 expression [189]. Not only this, in a pilot study in human volunteers, consumption of 68 g broccoli sprouts resulted in a significant inhibition of blood HDAC activity 3 h following intake [187]. SFN treatment induced changes in the gene expression of numerous genes in human colon cancer cell lines, although it remains unknown if these changes are consequence of modifications in their corresponding histone marks [127,191]. In support of this, squamous esophageal cells treated with SFN showed a marked increase in the RARβ expression in a similar manner as Trichostatin A (TSA) and 5-aza-CdR, two potent HDAC and DNMT inhibitors, respectively [192].

Allyl-isothyocyanate, one of the first compounds isolated from broccoli, was shown to increase acetylation of histones in mouse erythroleukemia cells [174]. In this study, this effect was independent of changes in HAT activity, which implicates HDAC inhibition as a possible mechanism for these results [174]. This has been confirmed by several other studies in which isothiocyanates have been shown to inhibit HDAC activity inducing histone acetylation and up-regulation of p21/Bax expression in various cancer cell lines (leukemia, esophageal squamous and prostate cancer cells) [128,193–195].

6.8. 3,3′-Diindolylmethane

3,3′-Diindolylmethane (DIM) is an active compound derived from the digestion of indole-3-carbinol, which is found in Brassica family of vegetables, such as broccoli or cauliflower. In a study to determine the HDAC inhibitory effects of DIM, Bhatnagar et al. found that this compound significantly inhibits the expression of HDAC1, HDAC2 and HDAC3 in colon cancer cells, which was associated with strong inhibition of anti-apoptotic protein survivin both in colon cancer cells and APCmin/+ mice [196]. Li et al. have recently provided insight into the mechanism responsible for HDAC1 inhibition. Using HT29 and SW620 colon cancer cell lines, the authors demonstrated that DIM selectively induces proteasome-mediated degradation of class I histone deacetylases (HDAC1-3 and HDAC 8), which resulted in increased p21 and p27 expression [197]. In another study, treatment of MCF-7 breast cancer cells with DIM prevented histone H4 acetylation at the *COX-2* gene promoter, thus inhibiting over-expression of this gene [198].

6.9. Isoflavone and soy peptides

Genistein is the major isoflavone present in soybeans. Accumulating evidence indicates that genistein possesses the highest histone modifying activity in comparison to the other isoflavones, biochanin A and diadzein (or its derivate equol). In the few available studies, genistein has shown to increase histone acetylation in esophageal squamous and prostate cancer cells [115,119,199]. In further support of this, several studies have revealed an increased activation of HAT after genistein treatment in renal and prostate cancers, and in some of these studies, this was associated with increased mRNA expression of *CREBBP*, *HAT1*, *PCAF* and *EP300* [118,119,200].

Three studies have evaluated the HDAC activity of genistein using in nuclear extracts from cancer cells indicating that this compound decreases the HDAC activity in squamous esophageal and renal cancer cell lines, but not in prostate cancer cells [115,118,119]. In addition, there is evidence suggesting that genistein inhibits the expression of SIRT1, one of the NAD^+ dependent histone deacetylases [201]. So, either by HAT activation or HDAC inhibition, genistein is clearly associated with activation of tumor suppressor genes (such as p21, p16, FOXA3a, PTEN, etc.) and inhibition of oncogenes (hTERT).

6.10. Resveratrol

Resveratrol is believed to play a significant role in the reduction of cardio-vascular events [202]. Multiple studies have shown that resveratrol is associated with activation of NAD^+ dependent histone deacetylase sirtuin 1 (SIRT1) and p300 in multiple in vitro and in vivo models [203–206]. In one of the key studies, Howity et al. showed that resveratrol intake could extend the lifespan of several yeast (Saccharomyces cerevisiae) and worms strains (Drosophila melanogaster) and have favorable effects against metabolic disorders including obesity and insulin resistance [203–205,207]. Although it is debated whether the direct SIRT1 activation-induced by resveratrol might be responsible for such effects [208–211], recent elegant animal studies have demonstrated that cancer preventive effects of resveratrol are significantly dependent on SIRT expression in APCmin/+ mice, suggesting the importance of SIRT1 activating effect as a key mechanism in resveratrol tumor prevention [212]. To further illustrate the molecular mechanism underlying how activated SIRT1 triggers cell death, it was demonstrated that SIRT1 negatively regulates expression of Survivin, which encodes an anti-apoptotic protein, by deacetylating H3K9 within the promoter of Survivin [213]. Additionally, it was shown that SIRT1 mediated BRCA1 signaling in breast cancer cells by inhibiting tumor growth through the repression of transcription of oncogenes or activity of oncoproteins [205,213]. In another recent study, it was demonstrated that resveratrol treatment also enhanced p53 acetylation and apoptosis in prostate cancer cells by inhibiting MTA1/NuRD complex [214]. Previously, it was demonstrated that resveratrol-induced SIRT1 activation lead to the modulation of PGC-1α functions in animals [215]. The authors suggested that resveratrol treatment ultimately impacted the regulation of energy homeostasis, which might be a crucial feature for its chemopreventive potential [215]. Since it is beyond the scope of this article to

Table 3
Polyphenols and microRNAs.

Dietary agent	Plant source	Analysis Method	Micro RNAs	Target gene	*In vitro* model	*In vivo* model	Concentration	Treatment duration	References
3,3-diindolylmethane	Broccoli	Microarray; qRT-PCR	miR-200 (a-c), let-7 (a-f), miR-146a	*ZEB1, EGFR*	Pancreas		25 μM	48 h	[225,226]
Curcumin	Turmeric	Microarray; qRT-PCR	miR-22, miR-199a*, miR-21, miR-200	*SP1, ESR1, PTEN*	Pancreas		1–10 μM	72 h	[222,223]
Epigalocatechin-3-gallate	Green tea	Microarray; qRT-PCR	miR-16	*BCLl2*	Liver		100 μM	24 h	[224]
Genistein (with daidzein, glycetein)	Soy	Microarray; qRT-PCR	miR-200 (a-c), let-7 (a-f), mir-27b, miR-146a	*ZEB1, ZBTB10, EGFR*	Pancreas; Uveal; Melanoma; Ovarian		25 μM	48 h	[225–228]
Isothiocyanates	Broccoli, wasabi	Microarray				Rat: lung cancer	500 mg/kg	28 days	[229]

describe the detailed effects of resveratrol on epigenetics and ageing, we direct the readers to some of the previously published reviews on the topic [216–218].

6.11. Quercetin

Quercetin, a potent anti-tumor dietary polyphenol, is predominantly present in citrus fruits and buckwheat. Quercetin has been shown to activate NAD^+ dependent histone deacetylase SIRT1 in yeast, but this effect was less pronounced compared to resveratrol [203]. Ruiz et al. evaluated the effect of quercetin on the TNFα mediated expression of interferon-g-inducible protein 10 (*IP-10*) and macrophage inflammatory protein 2 (*MIP-2*) genes in murine intestinal epithelial cells [219]. Treatment with quercetin was associated with inhibition of the HAT activity on the promoter region of these genes, which resulted in reduced gene expression [219].

6.12. Dihydrocoumarin

Dihydrocoumarin (DHC) is an active compound found in *Melitous officinalis* (sweet clover) that is widely used in food and cosmetic industries. DHC has recently identified as an inhibitor of the HDAC family of Sirtuins, which have a firmly established role in aging [220]. DHC disrupted heterochromatic silencing and inhibited yeast Sir2p and human SIRT1/2 deacetylase activity, which caused p53 acetylation and increase in apoptosis *in vitro* [220].

6.13. Sanguinarine

Sanguinarine (SGR) is commonly extracted from several plants such as bloodroot (*Sanguinaria canadensis*) or from the root, stem and leaves of the opium poppy. SGR has been shown to induce conformational changes by interacting with chromatin [221]. This compound potently inhibited HAT activity in rat liver and cervix cancer cell lines, and this was associated with dose-dependent decrease in H3/H4 acetylation. In addition, binding of SGR to chromatin inhibited H3K4 and H3R17 methylation, an epigenetic mark associated with transcriptional activation, more efficiently than H3K9 methylation, a marker for silent heterochromatin. Interestingly, SGR treatment was found to modulates global gene expression [221].

6.14. Other compounds with histone modification properties

In addition to the well-described effects of various dietary polyphenols on histone modifications described above, there are several other such compounds for which limited evidence exists for their ability to modulate histone modifications. Many of these additional compounds are not mentioned here, but are listed in Table 2.

7. Polyphenols and miRNA expression

MicroRNAs have been recently discovered as key regulators of gene expression. Although there is still limited evidence, recent reports have identified that dietary polyphenols can also modulate gene expression by targeting various oncogenic or tumor suppressive miRNAs. In the last section of this review, we will summarize the current evidence supporting the effect of dietay polyphenols on specific target miRNAs (Table 3 and Fig. 4).

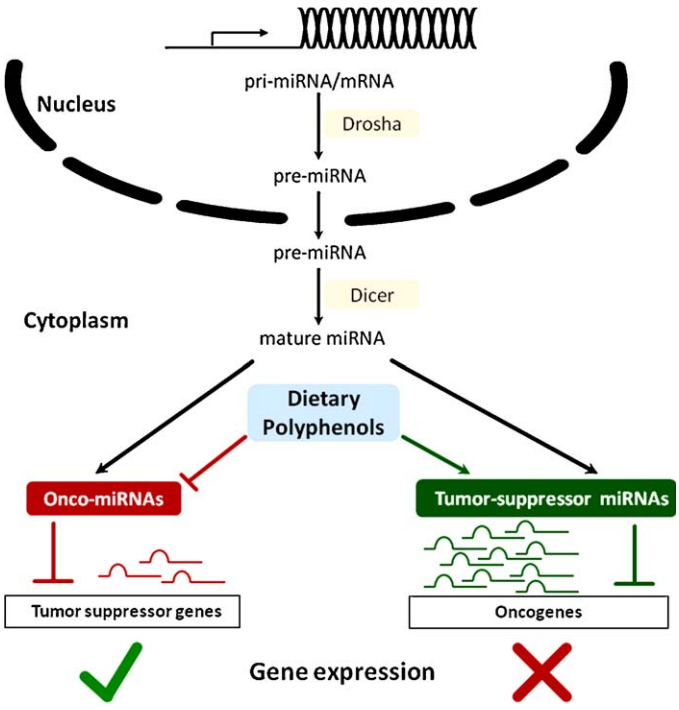

Fig. 4. Effect of dietary polyphenols on microRNA (miRNA) expression. miRNA are transcribed in the nucleus into primary miRNA (pri-miRNA) which is further cleaved by Drosha into precursor miRNA (pre-miRNA). Pre-miRNA is exported from nucleus to the cytoplasm and further processed by Dicer into miRNA duplex. Single strand of miRNA duplex (also called mature miRNA) leads this complex to mRNA cleavage or translation repression, which is dependent on miRNA:mRNA complementarity. Dependent on various factors, miRNA can have either an oncogenic role (called onco-miRNAs) if the target mRNA is a tumor suppressor gene, or a tumor suppressive role (tumor-suppressor miRNAs) if the target molecule is an oncogene. Dietary polyphenols can impact expression level of miRNAs and participate in gene expression regulation.

7.1. Curcumin

The antitumor activity of curcumin has been recently linked to changes in miRNA expression. Sun et al. treated BxPC-3 pancreatic cancer cell lines with curcumin and performed microRNA expression profile, showing significant changes in the level of expression of 29 miRNAs [222]. Upregulation of miR-22 was one of the most significant curcumin-induced changes. Functional studies showed that upregulation of miRNA-22 expression by curcumin or by transfection with miRNA-22 mimetics in the PxBC-3 pancreatic cancer cell line suppressed expression of two of its known target genes, *SP1* and *ESR1*. In other recently published study, Ali et al. have further analyzed potential of curcumin in treatment of pancreatic cancer in combination with Gemcitabine, a standard agent for the pancreatic cancer chemotherapy [223]. Using BxPC-3 and MIAPaCa cell lines, which show difference in gemcitabine-resistance, they demonstrated that treatment with either curcumin or curcumin-analogues potentiated apoptotic effects of gemcitabine, which resulted in induction of miR-200b/c and inhibition of miR-21 expression. In addition, the authors showed increased PTEN expression as a result of inhibition of miR-21 expression [223].

7.2. EGCG

EGCG has been recently found to modulate the miRNA expression in human hepatocellular carcinoma HepG2 cells. Tsang et al. performed microarray analysis in this cell line after EGCG treatment and found that this compound modified the expressions of 61 miRNAs [224]. miR-16, one of the miRNAs up-regulated by EGCG, is known to regulate the anti-apoptotic protein Bcl-2, and interestingly EGCG treatment induced apoptosis and down-regulated Bcl-2 in HepG2 cells. Transfection with anti-miR-16 inhibitor suppressed miR-16 expression and counteracted the EGCG effects on Bcl-2 down-regulation and also induction of apoptosis in cells.

7.3. Isoflavones: genistein and 3,3′-diindolylmethane (DIM)

Soybean isoflavones and DIM have been found to regulate the miRNA expression in pancreatic cancer cells. Li et al. recently compared the expression of miRNAs between gemcitabine-sensitive and gemcitabine-resistant pancreatic cancer cells and investigated whether the treatment of cells with these two dietary compounds could affect the expression of miRNAs [225]. The expression of the miR-200 and let-7 family was significantly down-regulated in gemcitabine-resistant cells, which showed epithelial-mesenchymal transition (EMT) characteristics. Interestingly, reexpression of miR-200 or treatment of gemcitabine-resistant cells with DIM or isoflavones (a combination of genistein, diadzein, and glycitein) resulted in the reversal of the EMT features, leading to epithelial morphology. These results indicate that natural compounds could function as miRNA regulators leading to the reversal of EMT phenotype, which is likely to be important for designing novel therapies for pancreatic cancer. The same group has further shown that treatment with the same compounds up-regulates miR-146a in pancreatic cancer cell, and this was associated with reduction in cell invasion and metastasis [226]. This effect was associated with downregulation of EGFR and NF-κB regulatory kinase interleukin 1 receptor associated kinase. Re-expression of miR-146a inhibited the invasive capacity of pancreatic cancer cells with concomitant down-regulation of EGFR and interleukin 1 receptor-associated kinase 1 (IRAK-1) further pointing the significance of polyphenol mediated anticancer effect [226].

Another study has shown that genistein inhibits cell growth and modulate the expression of miR-27a and one of its targets (gene zinc finger and BTB domain containing 10 or *ZBTB10*) in human uveal melanoma cell lines [227]. Further, in an observational study, Parker et al. observed that genistein is able to induce changes in miRNA expression in ovarian cancer cell lines [228].

7.4. Indole-3-carbinol and phenethyl isothiocyanate

Izzotti et al. recently published a study focused on the potential of natural compounds as chemopreventive agents after environmental cigarette smoke (ECS) exposure in animals [229]. In this study, microarray miRNA expression analysis was performed in the lungs of either ECS-free or ECS-exposed rats treated with the orally administered chemopreventive agents including indole-3-carbinol and phenethyl isothiocyanate (both found in cruciferous vegetables). Interestingly, none of the above chemopreventive agents appreciably affected the baseline microRNA expression in non-exposed lungs, indicating potential safety. However, all of them attenuated ECS-induced alterations to a variable extent and with different patterns, indicating potential preventive efficacy.

8. Summary and conclusions

There is traditional and widespread use of dietary polyphenols all around the world. While the anecdotal epidemiological evidence has historically supported the idea of different diet and good health, experimental evidence accumulated in the recent years from various pre-clinical and clinical studies clearly support the idea that dietary polyphenols have potentially beneficial effects on multitude of health conditions, including cancer. This review article provides a novel perspective on the potential chemoprevention by diet and dietary agents, as the extensive data summarized here suggest that beneficial effects of different dietary polyphenols may in part be attributable to their epigenetic properties, including changes in the DNA methylation pattern, regulation of histone modifications and changes in the expression of some miRNAs. Although the health effects of dietary polyphenols in humans are generally considered promising, there are definite challenges and limitations of the current data in better understanding the molecular mechanisms responsible for this effect, together with the possible interactions between different polyphenols and other dietary constituents. While *in vitro* models have enormously contributed to the understanding of polyphenols mediated regulation of the epigenetic network, there is still a paucity of *in vivo* data for the majority of these dietary compounds. Therefore, until sufficient preclinical and clinical data has been gathered on the epigenetic changes induced by some of the dietary polyphenols, one should be cautious while interpreting and extrapolating the significance of current *in vitro* evidence. Once such evidence is established, the next and more important step would be to determine the most effective doses of these 'dietary nutraceuticals' in order to obtain various beneficial effects in human subjects. Additional clinical work is required to examine the safety profile of various doses of dietary polyphenols, and more basic science studies are needed to improve our understanding of the molecular mechanisms underlying the chemopreventive effect of various dietary polyphenols. It is really exciting to witness that we have at least begun to explore the molecular mechanisms underpinning the "goodness" of certain diets and diet-related factors that has been in existence for centuries. The mere fact that currently hundreds of dietary polyphenols are being characterized from an "epigenomic" perspective clearly reflects our enthusiasm and trust we pose in the concept of safe and natural agents for cancer chemoprevention. Of course, the current evidence is thin and it is a long and treacherous road ahead of us; nonetheless, given the promise and potential of these polyphenols it is realistic

to fathom the possibility that some of these compounds may become integral for the cancer chemoprevention in future.

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