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Natural compound-derived epigenetic regulators targeting epigenetic readers, writers and erasers

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Abstract

Post-translational modifications can affect gene expression in a long-term manner without changes in the primary nucleotide sequence of the DNA. These epigenetic alterations involve dynamic processes that occur in histones, chromatin-associated proteins and DNA. In response to environmental stimuli, abnormal epigenetic alterations cause disorders in the cell cycle, apoptosis and other cellular processes and thus contribute to the incidence of diverse diseases, including cancers. In this review, we will summarize recent studies focusing on certain epigenetic readers, writers, and erasers associated with cancer development and how newly discovered natural compounds and their derivatives could interact with these targets. These advances provide insights into epigenetic alterations in cancers and the potential utility of these alterations as therapeutic targets for the future development of chemopreventive and chemotherapeutic drugs.

Graphical Abstract

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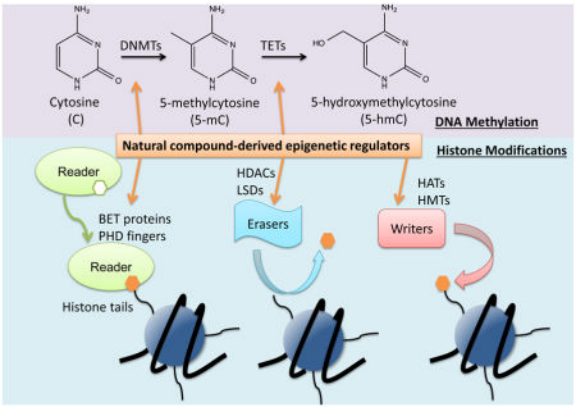
6. Conflict of interest statement

The authors declare no conflicts of interest.



Keywords

Epigenetics; post-translational modification; histone modifications; readers; writers; erasers

1. Introduction

The classical definition of epigenetics was initially proposed by Conrad Waddington as heritable changes of a phenotype without alterations in the DNA sequence [1]. Recently, epigenetic studies have been frequently applied to chromatin biology. These types of epigenetic alterations have been identified during the stages of carcinogenesis by specific patterns and characteristics [2]. Heritable epigenetic changes in gene expression are transmitted through both mitosis and meiosis without any change in the nucleotide sequence of the DNA [3]; however, this concept remains contentious. In addition, abnormal epigenetic modifications have been identified in various diseases, including different types of cancers. It is important to understand the epigenetic mechanisms underlying states from tumor initiation to heritability to define epigenetic transmission and understand how the misreading, miswriting and miserasing of chromatin contribute to oncogenesis and progression [4, 5]. In this review, we will focus on the link between oncogenesis and epigenetic aberrations. We will also discuss natural compound-derived epigenetic regulators as potentially novel pharmaceutical candidates targeting epigenetic readers, writers and erasers with the current preclinical and clinical uses of these compounds.

2. Epigenetics and chromatin biology

Generally, epigenetic changes can be categorized into several major biochemical mechanisms, including changes in DNA methylation, histone tail modification and non-coding RNA functions. In this review, we will focus on DNA methylation and histone tail modification.

2.1. DNA methylation

DNA methylation is a heritable modification of the DNA structure that involves adding a methyl group to the carbon 5 of cytosine (5mC) within the CpG dinucleotide. Regions of CpGs undergo methylation singularly or in clusters, so-called CpG islands [6]. Gene

silencing is usually due to the methylation of the promoter regions of the silenced genes [7]. The hypermethylation of the CpG islands in gene promoter regions has been commonly identified in cancer cells, resulting in the silencing of tumor suppressor genes [8, 9]. However, the overall hypomethylation of DNA has been reported in association with tumor progression. A balance of widespread hypomethylation and regional hypermethylation may be the key to human neoplasia [10]. The methylation of DNA is regulated by DNA methyltransferase (DNMT), including DNMT1, DNMT3a and DNMT3b. The DNMT3 family methylates the CpG dinucleotide through *de novo* pathways [11], and the DNMT1 family is reported to maintain the methylation during replication [8]. Additionally, methylated DNA can recruit members of the methyl CpG-binding domain (MBD) family, including methyl CpG-binding protein 2 (MeCP2) and MBD1 - 4 [12]. The MBD proteins can recruit histone deacetylases (HDACs), which act with DNA methylation to silence gene expression [13]. Discovery of Ten-eleven translocation (TET) enzymes helps to shed light on the mechanism of DNA demethylation. TET enzymes are dioxygenases which are dependent on 2-oxoglutarate (2OG) and Fe(II) to oxidize 5mC into 5-hydroxymethylcytosine (5hmC) [14–16].

2.2. Histone modifications

In addition to DNA methylation, epigenetic alterations also include histone modifications [17]. The mechanism by which epigenetic alterations are translated into meaningful biological signals is important; therefore, the identification of factors involved in creating, reading and removing epigenetic modifications has received increasing attention. For example, changes in DNA packaging, which can result from epigenetic changes, affect gene expression directly [18]. Chromatin is the scaffold for packaging the genome, which contains heritable materials as a macromolecular complex of DNA and histone proteins. One of the primary functions of chromatin is to recruit epigenetic regulators. Chromatin modifications affect non-covalent interactions among histones or between histones and DNA. A histone octamer is composed of an H3/H4 tetramer and two H2A/H2B dimers, which are wrapped with DNA to form the nucleosome. The major histone modifications include acetylation, methylation, phosphorylation, ubiquitination and sumoylation (addition of small ubiquitin-like modifiers) [19, 20]. In histone modification, there are various histone-modifying enzymes involved, including histone acetyltransferases (HATs), histone methyltransferases (HMTs), HDACs and histone demethylases (HDMs). These enzymes have different functions regarding the histone tails: HATs add acetyl groups; HMTs add methyl groups; HDACs remove acetyl groups; and HDMs remove methyl groups [21, 22]. Those histone modifications can either activate or repress transcription, depending on their location and type. Generally, histone modifications play a key role in maintaining the highly folded chromatin structure, which is closely linked to gene expression [23–25].

2.3. microRNA

MicroRNAs (mi-RNAs or miRs) are single-stranded small RNA molecules (~19–22 nucleotides long) involved in posttranscriptional gene regulation by either inhibition of translation or mRNA degradation [26, 27]. miRNAs have created new opportunities for the development of diagnostics, prognostics and targeted therapeutics in different cancer types including lung cancer [26], melanoma [27], prostate cancer [28] and others. These reviews

have summarized recent advances and approaches for identification of candidate miRNAs and their target genes in different types of cancers. For example, increased expression of enhancer of zeste homolog 2 (EZH2), a HMT of increasing importance, was associated with melanoma progression and overall patient survival and miRNA-31 overexpression resulted in down-regulation of EZH2. Down-regulation of miR-31 expression was also a result of epigenetic silencing by DNA methylation, and via EZH2-mediated histone methylation [29]. It appears that studying how epigenetic alterations involving DNA methylation, histone modifications and miRNA expression could provide new opportunity for the development of diagnostics, prognostics and targeted therapeutics in different cancer types.

3. Epigenetic readers, writers and erasers in the use of epigenetic modifications as therapeutic targets in cancer

Epigenetic modification is a dynamic process involving “epigenetic readers”, “epigenetic writers” and “epigenetic erasers”. In this review, we will focus on these effectors of epigenetic modification and introduce recent advances regarding their mechanisms of action, as well as their potential as chemopreventive and therapeutic targets of small molecules and natural compound-derived epigenetic regulators (Table 1).

3.1. Epigenetic readers

Epigenetic readers, also known as “chromatin readers”, possess specialized domains that recognize specific covalent modifications of the nucleosome and respond to upstream signals [30]. Mutations in chromatin reader domains abolish the chromatin-reading capacity of certain epigenetic regulators in various diseases, including cancers [31]. In addition, these epigenetic readers can identify different modified amino acids as well as the same amino acid in different states. For example, as mentioned before, lysine residues can undergo different covalent modifications, including acetylation, methylation and phosphorylation. To add more complexity, the same lysine residue can have several degrees of methylation: monomethylation, dimethylation and trimethylation. Epigenetic readers have several types of methyl-lysine-recognizing motifs, including tumor domains, chromodomains and the plant homeodomain (PHD), within proteins. Each type is in a family of proteins with varying specificities and preferred binding sites. The PHD finger is capable of detecting methylated histones. For instance, the PHD fingers of the proteins BHC80 and DNMT3L detect and bind unmethylated lysine residues [32, 33].

By contrast, if a lysine residue undergoes acetylation, it will dock to proteins with acetyl-lysine-binding residues such as bromodomains [34]. Bromodomains are highly conserved motifs that form a scaffold to facilitate DNA-templated processes. The knockout of particular bromodomain-containing proteins in mice induces embryonic lethality [35]. The bromodomain and extraterminal (BET) family of proteins includes four members: bromodomain-containing protein 2 (BRD2), BRD3, BRD4, and bromodomain testis-specific protein (BRDT). These proteins regulate transcription and cell growth, and the dysregulation of BET proteins has been demonstrated in cancers. For example, BRD2 is overexpressed in the lymphocytes of B-cell lymphoma patients [36]. BRD3 and BRD4 have been identified as drivers of proliferation in the malignancy NUT midline carcinoma [37]. These reports

suggest that BET proteins may be therapeutic targets in certain types of cancers using BET inhibitors, for example, the recently reported small molecules that specifically inhibit the BET family of proteins [37–39].

BET protein inhibitors are designed to block the interaction of the bromodomain with the acetylated residue by assembling a functional protein complex at the gene locus. The BET protein inhibitors developed to date include JQ1, I-BET151 and many others. For example, JQ1 can displace the aberrant fusion protein BRD4-NUT responsible for NUT midline carcinoma [37]. In addition, JQ1 prevents the binding of BRD4 to the upstream region of the MYC promoter region and subsequently reduces the expression of key oncogenes in myeloma cell lines [40, 41].

MBD proteins recognize methylated CpGs and bind to them to trigger methylation of H3K9, resulting in transcriptional repression [42]. Currently, the combination of 5- azacitidine and HDAC inhibitors has been used to treat hematological malignancies [43]. However, 5-azacitidine is a nonspecific demethylating agent and it may have the potential of demthylating promoter of silenced oncogenes and activate them to induce global hypomethylation. MBD1 appears to be a better candidate for cancer therapy. MBD1 recognizes methylated DNA and induces chromatin remodeling, regulating transcription by decoding methylated DNA. MBD protein has been reported to be involved in specific genes in different types of cancer. For instance, Imke *et al.* analyzed the involvement of MBDs and histone modifications on the regulation of CD44, Cyclin D2, GLIPR1 and PTEN in the prostate cancer cells DU145 and LNCaP, and the breast cancer cells MCF-7 [44]. Comparison of the different promoters show that MeCP2 and MBD2a repress promoter-specific Cyclin D2 in all cell lines, whereas in MCF-7 cells MeCP2 repressed cell-specific all methylated promoters [44]. However, the underlying mechanisms remain to be elucidated. If the abnormal DNA methylation cannot be recognized with inhibition of MBD proteins, the aberrant effect of DNA methylation status would be reduced to be less meaningful. Recently, Wyhs *et al.* has developed and compared fluorescence polarization and time-resolved fluorescence resonance energy transfer based high-throughput screening assays to identify small-molecule inhibitors of MBD2 and other DNA-protein interactions [45]. This include two known DNA intercalators, mitoxantrone and idarubicin, and two other inhibitory compounds, NF449 and aurintricarboxylic acid. They are reported to be nonspecifically inhibited the binding of a transcription factor to a methylated oligonucleotide [45].

3.2. Epigenetic writers

Epigenetic writers are proteins that are capable of adding modifications to DNA or histones. These proteins include DNMTs, HATs, HMTs and others. The epigenetic writers operate on the chromatin platform and introduce rapid, dynamic modifications in response to the environment.

DNMTs are actively involved in the modification of cytosines mostly in the context of CpG dinucleotides. It is a potential cancer therapeutic approach by reversing the hypermethylation of DNA promoter and gene silencing. There are two major DNA demethylating drugs, decitabine (DAC) and its analogue azacitidine, as irreversible

inhibitors of DNMT1 and DNMT3 [46, 47]. Efficacy of azacitidine has been applied in the treatment of higher-risk myelodysplastic syndromes (MDS) as a randomized, open-label, phase III study [48]. Transient exposure of DNA methylation inhibitors decitabine and azacitidine at a low dose decreased genome-wide DNA promoter methylation without immediate cytotoxicity such as DNA damage, apoptosis, and cell-cycle arrest [49].

HATs transfer an acetyl group from acetyl coenzyme A (acetyl-CoA) to the ε-amino group of lysine residues to form ε-N-acetyl-lysine in histones, thereby opening the chromatin. HATs are classified as type A or type B. Type A HATs are located in the nucleus and acetylate histones and chromatin-associated proteins. There are three families of enzymes, including Gcn5-related N-acetyltransferases (GNATs) and MYST (named after the four founding members, Sas3, Sas2, and Tip60). Type B HATs (comprising only HAT1) operate in the nucleus and cytoplasm to acetylate cytoplasmic histones, facilitating the translocation of these histones to the nucleus and subsequent deposition onto DNA [50]. HATs require the presence of actyl-CoA for catalytic activity. HAT inhibitors include bisubstrate HAT inhibitors, natural product HAT inhibitors and low-molecular-weight HAT inhibitors.

HMTs are classified as protein arginine methyltransferases (PRMTs) and protein lysine methyltransferases (KMTs). These enzymes transfer a methyl group from the cofactor S-adenosylmethionine (SAM) to arginine or lysine residues. The KMTs include DOT1-like histone H3K79 methyltransferase (DOT1L) containing the SET domain, a conserved catalytic domain also present in the PRMTs [52]. DOT1L is a key protein and an increasingly interesting therapeutic target in mixed-lineage leukemia (MLL)-rearranged leukemia. Daigle *et al.* reported that EPZ004777 acts as a selective inhibitor of the DOT1L H3K79 methyltransferase by imitating the cofactor SAM. EPZ004777 has anti-proliferative effects by blocking the expression of leukemogenic genes, with selectivity to kill cells bearing the MLL gene translocation [53]. However, the poor pharmacokinetic properties of this inhibitor limit its further application. Therefore, EPZ-5676, a second-generation DOT1L inhibitor, is undergoing clinical trials (ClincalTrials.gov identifier: NCT01684150) [54].

Another HMT of increasing importance is EZH2. EZH2 is the catalytic component of the polycomb repressive complex 2 (PRC2), and these factors are critically responsible for the methylation of H3K27, silencing various genes and altering biological processes [55]. This HMT is overexpressed in various types of cancers, including prostate, breast, kidney and lung cancers [56–59], which highlights the importance of developing methylation inhibitors targeting H3K27. For example, 3-deazaneplanocin A (DZNep), a molecule derived from SAM, decreases H3K27 methylation and induces apoptosis in cancer cells as an EZH2 inhibitor [60]. DZNep can reactivate silenced genes in cancer cells and selectively inhibit the trimethylation of H3K27me3 and H4K20me3 [61]. Most recently, several EZH2 inhibitors have been discovered with highly potent selectivity for EZH2 *in vivo* and *in vitro*, including EPZ-6438, GSK126 and EPZ005687 [62–64]. EPZ-6438 has already been utilized in clinical trials to treat patients with B-cell lymphoma (ClincalTrials.gov identifier: NCT01897571) and is the first EZH2 inhibitor that has been applied to solid malignant rhabdoid tumors [65].

3.3. Epigenetic erasers

Epigenetic erasers are proteins that are capable of removing modifications to DNA or histones that were produced by epigenetic writers to regulate gene expression. Epigenetic erasers include TET enzymes, HKMs and HDACs, targeting histones or other non-histone proteins.

TET family proteins help to uncover the mechanism of DNA demethylation, by limiting DNMT1's recognition to 5-hmc, so DNMT1 will not be able to perform the methylation of the DNA strand to maintain methylation status. The methylation is lost gradually in dividing cells in a passive manner [66]. Abnormal patterns of cytosine methylation have been observed in melanoma in association with tumor progression and drownregulation of the TET family genes [67]. However, TET mutation is rare in solid tumors and acquired mutations are missense mutations without certain consequences on TET protein in many cases [68, 69].

Histone lysine methylation (HKM) is a dynamic modification regulated by the recruitment of methyltransferases and demethylases [70, 71]. Recently, several histone demethylases were identified as being overexpressed in some human tumors. There are two well-studied families, including the lysine-specific demethylase (LSD) [72] and JmjC domain-containing lysine demethylase families [73, 74]. Members of the LSD family of proteins include the histone demethylase LSD1 (KDM1A) and the histone demethylase LSD2 (KDM1B). These proteins have oxidase-like domains, which have catalytic activities to remove the methyl group from histone lysines [75]. The LSD enzymes are highly expressed and could be valuable therapeutic biomarkers in prostate, breast and colorectal cancers [76–78]. Tranylcypromine, an enzyme monoamine oxidase (MAO) inhibitor, also inhibits LSD1 because of the similarity in the sequences of the catalytic domains of the LSD proteins and MAO enzymes [79, 80]. However, this non-selective characteristic reduces the application of this drug due to notable potential side effects. Therefore, derivatives of tranylcypromine have been developed. For example, ORY-1001 is in clinical trials for the treatment of relapsed or refractory acute leukemia (EudraCT Number: 2013–002447-29). Other studies have investigated a weak but selective LSD1 inhibitor that has *in vitro* and *in vivo* activity [81]. The JmjC domain-containing lysine demethylase family can remove methyl groups from mono-, di- and trimethylated lysines, in contrast to the LSD demethylases [74, 82]. GSK-J1, another promising compound, is an inhibitor of the JMJD3 subfamily. GSK-J1 binds competitively to the 2-oxoglutarate cofactor and chelates the metal in the active site [83].

HDACs are enzymes that remove the acetyl group from lysine residues in histones. Histone deacetylation causes transcription repression in the chromatin. HDACs are categorized as class I (HDAC1, HDAC2, HDAC3, and HDAC8), class IIa (HDAC4, HDAC5, HDAC7, and HDAC9), class IIb (HDAC6 and HDAC10), class III (SIRT1 to SIRT7) or class IV (HDAC11). SIRT1 to SIRT7, the seven sirtuins share a conserved NAD-binding and catalytic core domain but with different N- or C-terminal extensions. They are involved in transcription regulation, metabolic regulation, cell survival and many other biological pathways [84]. SIRT1 to SIRT7 could be promising therapeutic targets to treat cancers, because many sirtuin inhibitors have been reported to have anticancer activities [85]. Hu et

al. have summarized different classes of sirtuin inhibitors based on their structural categories and mechanisms of action [85]. For example, nicotinamide inhibit SIRT1 to SIRT3, SIRT5 and SIRT6. It has shown that nicotinamide can inhibit growth, promote apoptosis in leukemic cells and human prostate cancer cells [86–89]. Specific SIRT1 inhibitor cambinol can reduce tumorigeneisis in TH-MYCN transgenic mice by suppressing cancer cell proliferation [90].

In addition to histones, these HDACs can deacetylate non-histone proteins as well. For example, the tumor suppressor P53 protein is deacetylated by class I HDACs [91]. Recently, evidence has emerged indicating that HDAC expression has been altered in cancer cells and tumor tissues [92–94]. Therefore, HDACs are important targets for manipulating epigenetic modifications in cancer cells as a novel treatment strategy.

HDAC inhibitors bind to the catalytic site of HDACs and prevent these enzymes from binding to a substrate (histone or DNA). These HDAC inhibitors affect several biological processes, such as cell cycle arrest in the G1 stage, the inhibition of cell growth [95], cell differentiation and apoptosis [96], and HDAC inhibitor LBH589 (Panobinostat) induced sensitivity in combination with chemotherapeutic agents [97, 98].

HDAC inhibitors have been classified into four major classes based on their structures and different specificities for HDACs as follows: cyclic peptides, hydroxamates, short-chain fatty acids (SCFAs) and benzamides. For example, romidepsin (Isodax®) is a cyclic peptide that is isolated as a prodrug from *Chromobacterium violaceum*, a Gram-negative, anaerobic, non-sporing coccobacillus. Romidepsin is an HDAC-selective inhibitor that binds to the Zn^{2+} in the active site of HDACs. Romidepsin induces cell-cycle arrest and apoptosis, and this drug was approved by the US FDA to treat refractory cutaneous T-cell lymphoma in 2009 [99, 100] and peripheral T-cell lymphoma in 2011 [101, 102]. Cyclic peptides target human cancer cell lines *in vitro* and could be precursors for developing new drugs [103]. Hydroxamic acids are another important structural group, which includes trichostatin A (TSA) and others. TSA was the first compound found to inhibit HDACs [104] and has been reported to have a wide range of anti-cancer effects [105, 106]; however, TSA has been removed from clinical trials due to side effects. In 2006, vorinostat, suberoylanilide hydroxamic acid (SAHA), was approved by the FDA to treat cutaneous T-cell lymphoma [107] as a specific inhibitor of HDAC1, HDAC2, HDAC3 and HDAC6 [108].

Very recently, the HDAC inhibitors LBH589 (Panobinostat) and PXD101 (Belinostat) received FDA approval for patients with multiple myeloma and peripheral T-cell lymphoma, respectively. On July 3, 2014, the FDA granted accelerated approval for belinostat (BELEODAQ®; Spectrum Pharmaceuticals, Inc.), a HDAC inhibitor, for patients with relapsed or refractory peripheral T-cell lymphoma [109]. Novartis has developed oral and intravenous formulations of panobinostat (Farydak(®)), a HDAC inhibitor, for the treatment of cancer [110].

4. Natural compounds alter epigenetic modifications via epigenetic readers, writers and erasers - therapeutic targets

In this section, we will summarize and discuss certain epigenetic readers, writers, and erasers associated with cancer development and how newly discovered natural compounds and their derivatives could interact with these targets potentially resulting in cancer prevention and or treatment.

4.1. Phenolic compounds

There are various dietary polyphenolic phytochemicals with chemopreventive and chemotherapeutic effects due to the anti-oxidant and anti-inflammatory effects of these compounds in immune and cancer cells [111]. Based on their structures, phenolic compounds can be divided into two main classes: flavonoids and nonflavonoids. Phenolic compounds are commonly found in soybeans, spices and other sources. Currently, these natural dietary polyphenols, including curcumin and genistein, have been shown to reverse adverse epigenetic modifications that act on a chromosomal level. Phenolic compounds can reportedly reverse abnormal epigenetic modifications by regulating the activity of HDACs, HATs, HMTs, HDMs and DNMTs in cancer cells.

Curcumin—Curcumin is a well-characterized natural HAT inhibitor and a major active component from the rhizome of *Curcuma longa*. Curcumin has shown high efficacy in chemoprevention and as a chemotherapeutic in head, neck and lung cancers [112, 113]. Recently, it has been shown that curcumin decreased the expression of DNMTs and HDAC subtypes (HDAC4, 5, 6, and 8) and upregulated deleted in lung and esophageal cancer 1 (DLEC1), a tumor suppressor gene, in HT29 cells [114]. In leukemia cells, curcumin downregulated HDAC6, a class IIb deacetylase, as well as heat shock proteins (HSPs), and resulting in cell cycle arrest and apoptosis [115]. In addition, treatment with derivatives of the curcumin-like curcumin analog C66 attenuated diabetes-related increases in histone acetylation, HAT activity, and p300/CBP HAT expression [116]. In addition, treatment with derivatives of the curcumin-like curcumin analog C66 attenuated diabetes-related increases in histone acetylation, HAT activity, and p300/CBP HAT expression [116]. Treatment of curcumin significantly inhibited the HAT activity human hepatoma Hep3B cells, but not HDACs, contributing to the histone hypoacetylation [117].

EGCG—Epigallocatechin-3-gallate (EGCG) is one of the well-studied green tea polyphenols with many health beneficial biological effects including cancer chemoprevention and chemotherapy in prostate cancers [118], gastroenterological cancers [119] and others. Green tea polyphenols can activate p53 by inhibiting class I HDACs, resulting in acetylated Lys373 and Lys382 residues and inducing cell cycle arrest and apoptosis in LNCaP human prostate cancer cells [120, 121]. In addition, among these green tea polyphenols, EGCG has been identified as an inhibitor of HAT, whereas other polyphenol derivatives have lower HAT inhibitory effects, including catechin, epicatechin, and epigallocatechin [122]. EGCG is with more specificity for HATs but less specificity for other epigenetic writers, including HMTs; the inhibition of HAT by EGCG reduced NF-κB activity and decreased the binding of p300 to the IL-6 promoter, subsequently suppressing

pro-inflammatory response [122]. EGCG treatment decreased global DNA methylation levels, and HDAC activity in human skin cancer A431 cells with reactivation of silenced tumor suppressor genes, Cip1/p21 and p16INK4a [123]. Combination of EGCG with the HDAC inhibitor, TSA, showed a synergistic effect of reactivation of ERα expression in ERα-negative breast cancer cells. EGCG is reported to remodel the chromatin structure of the ERα promoter leading to ERα reactivation [124]. Combination of EGCG with cisplatin significantly inhibited proliferation, and induced cell cycle arrest in G1 phase in non-small-cell lung cancer A549/DDP cells. They are reported to inhibit DNMT activity and HDAC activity, reversal of hypermethylated status and downregulated expression of GAS1, TIMP4, ICAM1 and WISP2 genes [125]. Very recently, EGCG is reported to reverse the expression of various tumor-suppressor genes (TSGs) by inhibiting DNMTs and HDACs in human cervical cancer cells [126].

In addition, EGCG has impacts on Bmi-1 and enhancer of zeste homolog 2 (Ezh2), two key PcG proteins as epigenetic regulators of chromatin. It is reported that EGCG reduced Bmi-1 and Ezh2 level in SCC-13 cells. In addition, a global reduction in histone H3 lysine 27 trimethylation was reported to be associated with reduction in survival [127]. EGCG with or without 3-deazaneplanocin A (DZNep) co-treatment in skin cancer cells reduce the level of PcG proteins including Ezh2, Bmi-1 and others. In addition, HDAC1 is also reduced, associated with increased tumor suppressor expression and reduced cell survival rates [128]. In a most recent report, green tea polyphenols (GTP) and EGCG induced TIMP-3 mRNA and protein levels by epigenetic silencing mechanism(s) involving increased EZH2 activity and class I HDACs in breast cancer cells [129]. In skin cancer cells, Bmi-1 is observed with increased expression contributing to skin cancer cells survival. EGCG treatment suppressed skin cancer cells survival [130].

Genistein—Genistein is a phytoestrogen derived from soybeans and other sources. This compound has been reported to play an important role in the post-translational modification of histones. In LNCaP human prostate cancer cells, genistein inhibited HDAC6, a heat shock protein Hsp90 deacetylase, which in turn decreased the level of the androgen receptor (AR) by regulating the ability of the HDAC6-Hsp chaperone to stabilize the AR protein [131].

Quercetin is a dietary polyphenol derived primarily from buckwheat and citrus. Quercetin inhibited HAT activity and subsequently reduced the recruitment of cofactors to the chromatin associated with pro-inflammatory genes in epithelial cells [132]. In addition, quercetin inhibited the expression of the epigenetic markers HDAC-1 and DNMT1 to induce cell cycle arrest and apoptosis, thereby blocking invasion and angiogenesis [133].

Resveratrol—Resveratrol is a polyphenol derived from plants such as blueberries, cranberries, and grapes. Resveratrol has exhibited anti-inflammatory and other effects via the regulation of pathways such as the cell cycle, apoptosis, angiogenesis and tumor metastases [134]. Recent studies show that resveratrol can downregulate metastasis-associated protein 1 (MTA1), which inactivates PTEN in prostate cancer cells. In addition, resveratrol could also activate the nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase SIRT1 as one of the key features. Resveratrol activates sirtuins, as the class III HDAC. It's reported that resveratrol could induce cell cycle arrest in the G1 phase and it

inhibits gastric cancer in a SIRT1-dependent manner [135]. *In silico* docking models was used to study resveratrol's interaction with different types of HDACs [136]. In vitro analyses of solid tumor cell lines showed that resveratrol inhibited all eleven human HDACs of class I, II and IV in a dose-dependent manner. Resveratrol promotes acetylation and reactivation of PTEN via inhibition of the MTA1/HDAC complex, resulting in inhibition of cell survival pathway such as the Akt pathway [137].

4.2. Organosulfur compounds

Organosulfur compounds are organic compounds that contain a variety of sulfur functional groups, such as C-S double and triple bonds, thioethers, disulfides, polysulfides, sulfonic acids, esters, amides, sulfuranes and persulfuranes [138]. Many organosulfur compounds have been investigated for roles in epigenetic regulation. For example, sulforaphane (SFN) has been widely proven to be involved in global DNA demethylation, HDAC inhibition, and mi-RNA modulation [139–142]; phenethyl isothiocyanate (PEITC) inhibits both HDAC and CpG methylation in various genes [143–145]; and diallyl disulfide (DADS) enhances histone acetylation by inhibiting HDAC [146, 147].

SFN—SFN is an organosulfur compound containing an isothiocyanate group and can be found in many cruciferous vegetables. SFN has proapoptotic and antiproliferative properties [148]. Its diverse biological effects also include anticancer effects, cell cycle arrest, and the induction of heme oxygenase and phase-2 detoxifying enzyme [149]. SFN mediates its anticancer effects primarily via epigenetic mechanisms [149], which may include the inhibition of HDAC, which increases global and local histone acetylation [150, 151], the induction of demethylation [139] and the modulation of miRNA [142].

When tested in human embryonic kidney 293 cells, SFN was found to inhibit HDAC activity, increase histone acetylation, and increase the number of acetylated histones bound to the P21 promoter, thus increasing p21 (Cip1/Waf1) expression [152]. SFN has been demonstrated to prevent the TPA-induced neoplastic transformation of mouse epidermal JB6 (JB6 P+) cells by inhibiting the activity of HDACs, especially HDAC1, HDAC2, HDAC3 and HDAC4 [140]. In a clinical study, after the consumption of 68 g of broccoli sprouts containing approximately 105 mg of SFN, HDAC activity was significantly decreased in the peripheral blood mononuclear cells of all three subjects [153].

SFN has demonstrated DNMT-inhibiting effects. Meeran *et al.* first reported that SFN inhibits DNMT1 and DNMT3A in MCF-7 and MDA-MB-231 human breast cancer cells [154]. SFN was found to regulate the MSTN signaling pathway in porcine satellite cells by significantly inhibiting HDAC activity and DNMT1 expression [155]. SFN was observed to inhibit proliferation in MCF-7 and MDA-MB-231 breast cancer cells and to downregulate DNMT1 by 0.75-fold, DNMT3A by 0.0185-fold, and DNMT3B by 1.174-fold [156].

Recent studies have revealed the role of SFN in modulating miRNA. SFN was found to inhibit DCIS stem cell signaling by increasing exosomal miR-140 and decreasing exosomal miR-21 and miR-29 [142]. By inducing miR-200c, SFN inhibits the epithelial-mesenchymal-transition and metastasis [157]. In a Chip-Seq assay, SFN was found to reduce miR-29B-1 expression [158].

PEITC—Similar to SFN, PEITC contains an isothiocyanate functional group and is widely found in a variety of cruciferous vegetables. PEITC exhibits the dual functions of HDAC inhibition and CpG demethylation in various genes [143–145].

Generally, PEITC acts as an HDAC inhibitor. In the LNCaP cell line, PEITC upregulated p21 gene expression by significantly enhancing histone acetylation via the inhibition of HDAC activity and by inducing histone methylation modifications, resulting in chromatin remodeling [159]. Wang LG *et al.* also found that PEITC increases histone acetylation in LNCaP cells by decreasing the activity of HDACs, especially HDAC1 [160].

Moreover, PEITC demethylates the promoter and restores the expression of glutathione S-transferase Pi 1 (GSTP1) in both androgen-dependent and androgen-independent LNCaP cancer cells [160]. PEITC has also been demonstrated to have hypomethylation potential *in vivo*. In TRAMP mice that were given an oral dose of 15 μmol of PEITC daily for 13 weeks, prostate tumorigenesis was significantly retarded due to the demethylation of the MGMT promoter [145].

DADS—DADS, a dietary disulfide, is found at high concentrations in garlic. DADS have been shown to enhance histone acetylation [146, 147]. Bioinformatics research suggests that both DADS and SFN have structural features compatible with HDAC inhibition [161].

After metabolic conversion, DADS is gradually converted to its main active metabolites, S-allylmercaptocysteine (SAMC) and allyl mercaptan (AM) [162, 163]. DADS and SAMC were found to induce the differentiation of erythroleukemic cells by enhancing histone acetylation [164]. *In vitro*, AM was a more potent inhibitor of HDAC than the precursor compounds DADS and SAMC, leading to the hyperacetylation of H3 and H4, enhancement of the association of ac-H3 with the p21 promoter and upregulation of p21 [165]. DADS treatment can induce transient histone hyperacetylation, p21 induction and apoptosis in various types of cancer cells [166]. In Caco-2 and HT-29 cells, 200 μM DADS was found to significantly inhibit HDAC activity, inducing histone hyperacetylation and increasing $p21^{waf1/cip1}$ expression [167]. In *in vivo* experiments, the injection of DADS (200 mg/kg b.w.) into male rats was reported to result in increased histone acetylation in normal hepatocytes and colonocytes [168].

4.3. Triterpenoids

Triterpenoids, which are synthesized by the cyclization of squalene, are metabolites of isopentenyl pyrophosphate [169]. At least 20,000 triterpenoids exist in nature. To date, many natural fruits and medicinal plants such as apples, ballon flower, bearberry, blueberries, boswellia, cranberries, figs, ginseng, holy basil, lavender, mango, onions, olives, reishi, and rosemary, among others, have been found to be rich natural sources of triterpenoids [170]. Increasing evidence demonstrates that triterpenoids are involved in a variety of biological activities, with anti-proliferative, pro-apoptotic, anti-oxidative, anti-inflammatory, anti-allergic, anti-microbial, anti-viral, anti-pruritic, anti-angiogenic, anti-invasive, and anti-tumor properties [170–172]. Nonetheless, it is not well understood whether triterpenoids act on epigenetic regulators and/or how triterpenoids interact with epigenetic regulators to exert their biological functions. We herein summarize some studies that illustrate the potential of

triterpenoids to produce epigenetic alterations that protect against a variety of human diseases, including cancer.

Oleanolic acid—Oleanolic acid (OA, 3β-hydroxyolean-12-en-28-oic acid) is a pentacyclic triterpenoid that can be obtained from approximately 1,600 different plants [173]. Of note, OA is used as the backbone for a new synthetic oleanane triterpenoid, 2-cyano-3, 12-dioxooleana-1, 9(11)-dien-28-oic acid (CDDO) and its derivatives, such as CDDO-methyl ester (CDDO-Me) and CDDO-imidazole (CDDO-Im) [173, 174]. OA is a typical triterpenoid that exerts protective effects on the liver, heart, and stomach and functions as an anti-viral, anti-oxidative, anti-inflammatory, and anti-cancer agent [174, 175]. A very recent report revealed that miR-122 is a potential target in cancer prevention [176]; miR-122 has anti-tumor activity, and its promoter is hypermethylated in liver cancer cells [177, 178]. OA treatment enhanced miR-122 expression, thereby suppressing the growth of lung cancer cells and lung cancer xenografts in mice. OA displays anti-diabetic activity by reducing hyperglycemia [179]. Zhou and his colleagues determined the hypoglycemic mechanisms of OA in a mouse model of type 2 diabetes [180]. The administration of OA to diabetic mice increased phosphorylation and acetylation at lysines 259, 262, and 271 in Forkhead box O1 (FoxO1). These modifications of FoxO1 were accompanied by an increase of HAT1 and the inhibitory phosphorylation of HDAC4 and HDAC5. Notably, the effect of OA lasted up to 4 weeks after suspending OA treatment.

Ursolic acid—As an isomer of OA, ursolic acid (UA; 3b-hydroxy-12-urs-12-en-28-oic acid), is present in variety of fruits and medicinal herbs, including apple peels, cranberry, bearberry, lavender, peppermint leaves, and holy basil [181]. UA has been used only as an emulsifying agent in pharmaceutics, cosmetics, and food and thus has not historically attracted much attention; however, robust studies have been performed since the discovery that UA protects against inflammation from carrageen-induced paw edema [182]. To date, UA has been found to be useful in treating various pathological conditions, including oxidative stress, DNA damage, hyperlipidemia, and inflammation [181–183]. UA is one of the triterpenoids exhibiting anti-cancer activity through diverse signaling pathways, such as the apoptotic pathway [184]. In a study identifying the effect of UA on human acute myeloid leukemia HL-60 cells, the cytotoxicity of UA was attributed to increased acetylation of histones H3, H3K18, and H3K9 and decreased expression of HDAC 1, 3, 4, 5, and 6 [185]. In human glioma cells, UA induced apoptosis by decreasing levels of miR-21, which is regulated by DNA methylation [186, 187]. The reduction in miR-21 activated a cell death pathway via caspase-3 and programmed cell death 4 (PDCD4).

CDDO and its derivatives—CDDO is a synthetic oleanane triterpenoid (SO) and the most potent triterpenoid with activity in the nanomolar and/or picomolar range. CDDC was developed by the chemical modification of three sites in OA, the C-28 carboxyl group, the C-12-C-13 double bond, and the C-3 hydroxy group [188]. Moreover, additional changes at the C17 of CDDO have yielded several types of derivatives, such as a methyl ester (CDDO-Me), imidazolides (CDDO-Im), amides (methyl amide, CDDO-MA; ethyl amide, CDDO-EA; trifluoroethyl amide, CDDO-TFEA), and a dinitrile (di-CDDO) [188, 189]. In addition to the use of SOs for treating cancer, a growing list of *in vitro* and *in vivo* data demonstrate

that they are involved in a broad spectrum of biological mechanisms, including differentiation, proliferation, growth arrest, apoptosis, and inflammation [190]. After SOs were first synthesized in the late 90s [191], the role of SO in epigenetic modulation was quickly discovered. Treatment of acute promyelocytic leukemia ATRA-sensitive NB4 and resistant MR2 cells with CDDO and all-trans-retinoic acid (ATRA) increased H3-Lys9 acetylation in the RARβ2 promoter. This histone acetylation induced expression of the peroxisome proliferator-activated receptor-γ (PPARγ), resulting in enhanced apoptosis and differentiation [192]. CDDO-Me has stronger anti-cancer potency than CDDO [193]. An investigation demonstrated that CDDO-Me inhibits proliferation and induces apoptosis in human pancreatic cancer cells by downregulating hTERT expression, which was mediated through a decrease in DNMT1 and DNMT3a, the demethylation of CpGs in the hTERT promoter, and a reduction in acetylated H3-Lys9, acetylated H4, dimethyl-H3-Lys4, and trimethyl-H3-Lys9 at the hTERT promoter [194].

Boswellic acid—Boswellic acid (BA), the most abundant exudate from the gum resin of *Boswellia serrate*, has been used in India to treat inflammatory disorders such as arthritis and inflammatory bowel disease because of its potent anti-oxidative capacity [195, 196]. Based on these positive effects, clinical trials have been conducted using BA to treat Crohn's disease, chronic colitis, ulcerative colitis, and brain tumors [197]. BA consists of four components, β-boswellic acid (β-BA), acetyl-β-boswellic acid (ABA), 11-keto-boswellic acid (KBA), and 11-keto-β-acetyl-11-keto-β-boswellic acid (AKBA) [198]. KBA and AKBA are among the main compounds responsible for the pharmacologic effects of BA. AKBA has been found to have anti-tumor effects in several forms of cancers in the brain, bone marrow, colon, liver, pancreas, and prostate [199, 200]. The mechanism for AKBA's cytotoxicity to cancer cells seems in part to be epigenetic modulation. Human colorectal cancer SW48 cells that have undergone AKBA-induced growth inhibition and apoptosis exhibit a loss of methylation in a large number of CpG sites [201]. In addition, AKBA treatment caused two tumor suppressor genes, SAMD14 and SMPD3, to be demethylated and DNMT activities to decrease in SW48 and SW480 cells. The same group also demonstrated that AKBA increased let-7b, let-7i, miR-200b, and miR-200c in human colorectal cells and nude mice transplanted with HCT116 cells, leading to the inhibition of cell growth, proliferation, and migration, as well as the induction of apoptosis in colorectal cancer [202].

4.4. Ginsenosides

Ginseng (Panax ginseng C.A. Meyer) is a very common medicinal herb and food supplement in Asia, particularly in China, Japan, and South Korea, and is even currently used in Western countries [203, 204]. Ginseng has long been used to maintain physical health and combat aging and is a main ingredient in traditional medicine. Ginsenosides are triterpenoid saponins, the primary active components of ginseng [205]. Diverse structural modifications classify ginsenosides into three groups: i) the oleanolic acid group (Ro); ii) the 20(S)-protopanaxadiol group (e.g., Ra, Rb, Rc, Rd, Rg3, Rh2 and Rs); and iii) the 20(S)-protopanaxatriol group (e.g., Re, Rf, Rg1, Rg2 and Rh1) (G-6, 7). Each ginsenoside plays a unique role in human disease. As part of a chemopreventive and anti-cancer regimen, ginsenosides have many advantages, including fewer side effects, low rates of recurrence,

and a reduction in cancer-related symptoms [206]. As a result, such regimens increase the cure rate in cancer patients.

Rh2 is a member of the 20(S)-protopanaxatriol group of ginsenosides. The treatment of human non-small cell lung cancer A549 cells with Rh2 upregulated 44 miRNAs, including let7 and miR-196, and downregulated 24 miRNAs, such as miR-193 [207]. Because let-7, miR-196, and miR-193 are miRNAs regulated by epigenetic mechanisms, these results suggest that Rh2 may modulate epigenetic alterations in lung cancer cells. Indeed, Rh2 increased HDAC4 expression in human liver carcinoma HepG2 cells [206]. The increased HDAC4 caused the repression of AP-1 and MMP3 expression, leading to reduced survival and migration. Rg2 may affect the epigenetic regulation of genes, as seen from a study of brain tumors. Human glioma cells treated with Rg2 displayed growth inhibition and apoptosis through increased miR-128 expression [208]. The repression of miR-128 induces upregulation of Bim-1, which is highly expressed in cancer cells [209].

Unlike Rh2, the relevance of Rg1 to epigenetic pathways has been confirmed through its effects on angiogenesis. Rg1 is another bioactive member of the 20(S)-protopanaxatriol ginsenosides. In human umbilical vein endothelial cells (HUVECs), Rg1 repressed the expression of miR-214, accelerating eNOS expression and angiogenesis [210]; however, miR-214 is a negative regulator of EZH2, which is elevated in cancers [211]. Lately, it has been proposed that miR-15b inhibits 5-hydroxymethylcytosine (5hmc) by decreasing TET3 [212]. The levels of 5hmc are low [213, 214] during tumor progression but are high in low-grade brain tumors and liver cancer patients with high survival rates and low recurrence rates [215, 216]. Notably, Rg1 downregulated miR-15b, which is involved in angiogenesis in HUVECs [217].

Compound K, a metabolite of 20(S)-protopanaxadiol ginsenosides, impaired the RUNX3 re-expression-induced growth of human colorectal cancer HT-29 cells through the demethylation of a RUNX3 promoter, which is known to be hypermethylated in colon cancer cells and patients. The decrease in RUNX3 methylation was associated with the decreased expression and activity of DNMT1. In addition, an IC50 concentration of Compound K acetylated the RUNX3 promoter with diminished HDAC1 expression and HDAC activity, and increased the acetylation of histones H3 and H4, which arrested the cell cycle at the G0/G1 phase [218].

Two stereoisomers of Rg3, 20(S)-Rg3 and 20(R)-Rg3, are members of the protopanaxadiol group [219]. Recently, it was found that Rg3 acts as an HDAC3 inhibitor in melanoma cells [220]. The treatment of human melanoma A375 and C8161 cells with Rg3 produced cell cycle arrest at the G0/G1 phase through decreased HDAC3 expression and increased acetylation of p53 on Lysine-373 and Lysine-382. These epigenetic events led to a reduction in PRB, cyclin E, cyclin D1, CDK2, and CDK4 and the induction of p21 expression. In these studies, Rg3 administration to nude mice inoculated with A375 cells conferred lower expression levels of HDAC3 and higher levels of acetylation of p53 (Lys-373/Lys-382), which resulted in reduced xenograft tumor volume and tumor weight.

4.5. Other phytochemicals and their derivatives

3, 3′-Diindolylmethane—3, 3′-Diindolylmethane (DIM) is a byproduct of the digestion of indole-3-carbinol (I3C), which is found in cruciferous vegetables, including broccoli, cabbage, kale and Brussels sprouts. DIM acts as an anticancer agent by inducing cell cycle arrest and apoptosis and is undergoing clinical trials [221]. DIM can selectively inhibit class I HDACs by inducing their proteasome-mediated degradation, revealing the potential of DIM as a chemoprevention agent [222]. Both DIM and I3C counteract the effects of enterotoxin B (SEB)-induced activation of T cells in mice as inhibitors of class I HDACs, but not class II HDACs [223]. Notably, DIM, but not I3C, specifically decreases HDAC2 activity in LNCaP and PC-3 prostate cancer cells [224]. Recently, the effects of DIM and SFN on genome-wide promoter methylation have been tested in normal prostate epithelial cells and prostate cancer cells, and the results indicated that DIM reversed abnormal methylation in cancer-associated genes [225]. All of these investigations suggest that DIM can exert cancer preventive and even therapeutic effects via the reversal of abnormal epigenetic alterations.

Valproic acid—SCFAs are produced from the fermentation of dietary fiber in the colon [226]. SCFAs can be categorized based on the number of lipids and include butyric and valeric acid. Valproic acid (VPA) was first synthesized in 1882 by Burton as an analog of valeric acid. VPA has been shown to be an HDAC inhibitor in several clinical studies when used in combination with all-trans retinoic acid to treat acute myeloid leukemia (AML) patients with intensive chemotherapy [227]. VPA has been reported to show anti-leukemic effects in combination with other demethylating agents such as decitabine and 5-azacitidine (5-AZA) [228]. In addition, VPA is in a phase III clinical trial as an HDAC inhibitor in solid tumors [229]. Those trials illustrate the emerging importance of targeting epigenetic erasers in the classical standard combination chemotherapy [229]. Recently, VPA has been shown to attenuate cardiac hypertrophy and fibrosis by inhibiting HDACs to acetylate the mineralocorticoid receptor (MR) in spontaneously hypertensive rats [230]. Amide derivatives of valproate are being considered as potential follow-up compounds, including valproyl glycinamide, 3-methylbutanamide or isovaleramide and SPD421 (DP-valproate) [231, 232].

Anacardic acid—Anacardic acid, a bioactive phytochemical found in the shell of nuts from *Anacardium occidentale*, is a non-competitive inhibitor of p300, PCAF and Tip60 [233]. Anacardic acid is structurally related to salicylic acid. Anacardic acid still has limited applications, similar to most natural compounds, because of its low cell permeability [234]. In contrast to anacardic acid, garcinol is a highly permeable but non-specific HAT inhibitor that is extracted from the rinds of the *Garcinia indica* fruit [235]. This non-specific nature of garcinol increases toxicity; therefore, more specific, less toxic HAT inhibitors, LTK14 and LTK15, were derived from garcinol [236].

5. Conclusions and perspectives

Individual phenotypes appear to be a complex record of interactions with the environment, that is, lifelong exposure to stimuli and the consequential reactions of the genome and

epigenome. Recently, understanding how epigenetic mechanisms record environmental changes within individuals and contribute to the development of various types of diseases including cancers has gained increasing importance. These studies enhance our understanding and ability to manipulate the epigenome, especially to reverse abnormal epigenetic modifications and restore normal biological function.

Natural compounds in the diet or herbal medicinal phytochemicals are promising epigenome modifiers targeting epigenetic readers, writers and erasers resulting in diseases prevention including cancer chemoprevention or chemotherapeutic treatment. In addition to these characteristics as epigenetic regulators, natural compounds are generally characterized with low toxicity and easy access in daily life. All these advantages have placed bioactive natural compounds as important health beneficial and potential diseases prevention agents including cancer chemoprevention. Our current review provides a brief insight into some selected dietary phytochemicals on their potential epigenetic targets. A summary of these alterations is provided in Table 1, which includes accumulating evidence of dietary chemopreventive compounds' role in preventing and reversing these abnormal epigenetic modifications in cell culture or animal model systems. Understanding the potential differences in different cell types and organs will be crucial in designing future personalized dietary strategy in diseases prevention including cancer. Furthermore, combination of some of these selective epigenetic regulators with more targeted epigenetic drugs could potentially yield synergistic effects in cancer prevention and therapy. For instance, butyrate, an HDAC inhibitor, in combination with a dietary vitamin A derivative, is used in the treatment of acute promyelocytic leukemias [238]. Some epigenetic drugs are currently used in combination with cancer chemotherapeutic agents in reversing transcriptional resistance mechanisms in cancers [239]. In addition, although miRNA and long non-coding RNA are not the focus of this review, they have been important targets of many natural dietary compounds, including polyphenols [240].

In conclusion, it is important to fully understand the biological functions and detailed mechanisms of action of chromatin proteins. Further exploration of natural compounds alone or in combination will be important to move forward evidence-based clinical trials using natural products as modifiers targeting epigenetic readers, writers and erasers resulting in cancer chemoprevention or even chemotherapeutic treatment.

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Abbreviations

AM	allyl mercaptan
AML	acute myeloid leukaemia
BA	boswellic acid

BET	bromodomain and extraterminal family of proteins
BRD	bromodomain-containing protein
BRDT	bromodomain testis-specific protein
CDDO	2-cyano-3, 12-dioxooleana-1, 9(11)-dien-28-oic acid
DADS	Diallyl disulfide
DNMT	DNA methyltransferase
DOT1L	DOT1-like histone H3K79 methyltransferases
EZH2	enhancer of zeste homolog 2
FDA	Food and Drug Administration
FoxO1	forkhead box O1
HAT	histone acetyltransferase
GSTP1	glutathione S-transferase Pi 1
GNATs	Gcn5-related N-acetyltransferases
HDAC	histone deacetylase
HDM	histone demethylases
HMT	histone methyltransferase
KMT	lysine methyltransferase
HSP	heat shock proteins
LSD1	lysine-specific demethylase 1
MR	mineralocorticoid receptor
MBD	methyl CpG-binding domain
MeCP2	methyl CpG binding protein 2
OA	Oleanolic acid
PEITC	Phenethyl isothiocyanate
PHD	plant homeodomain
PRMTs	protein arginine methyltransferases
PTM	post-translational modification
PRC2	polycomb repressive complex 2
PDCD4	programmed cell death 4

SCFAs	short-chain fatty acids
VPA	valproic acid
SAM	S-adenosylmethionine
SAMC	S-allylmercaptocysteine
SFN	Sulforaphane
TSA	trichostatin A
TET	Ten-eleven translocation enzymes
UA	ursolic acid

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Table 1

Natural dietary compounds and derivatives with targets at epigenetic writers, readers and erasers in cancers.

Compound	Epigenetic targets	Phase	Cancer types	Reference
Curcumin	Decrease expression of DNMTs, HDACs	Preclinical	Colon, leukemia, head, neck and lung	[112–116]
EGCG	Decrease expression of class I HDACs and HATs; decrease EZH2 protein level; decrease DNMT activity	Preclinical	Prostate, skin, breast and cervical cancers	[121, 123–127]
Genistein	Decrease expression HDAC6	Preclinical	Prostate	[131]
Quercetin	Decrease expression of HDAC1 and DNMT1; decrease HAT activity	Preclinical	Prostate	[132, 133]
Resveratrol	Inhibit the MTA1/HDAC complex	Preclinical	Prostate	[134, 137]
Sulforaphane	Decrease HDACs and DNMTs activity	Preclinical	Breast and skin	[140, 153–156]
Phenethyl isothiocyanate	Decrease HDACs and CpG methylation	Preclinical	Prostate, colon,	[143–145, 162–168]
Oleanolic acid	Increase HAT1 activity; decrease phosphorylation of HDAC4 and HDAC5	Preclinical	*type 2 Diabetes*	[180]
Ursolic acid	Decrease expression of HDAC 1, 3, 4, 5, and 6	Preclinical	human acute myeloid leukemia	[185]
Boswellic acid	Loss of methylation in lots of CpG sites; decrease DNMTs activities	Preclinical	human colorectal cancer	[201, 202]
Ginsenosides Rh2	Rh2 increased HDAC4 expression	Preclinical	human liver carcinoma HepG2 cells	[206]
Ginsenosides Rg1	Rg1 repressed expression of miR-214 and miR-214 is a negative regulator of EZH2	Preclinical	human umbilical vein endothelial cells	[210, 211]
Compound K	Decrease HDAC1 and DNMT1 activities	Preclinical	human colorectal cancer cells	[218, 230]
3, 3′-Diindolylmethane	Decrease HDACs activities	Preclinical	Prostate cancers cells	[222]
Valproic acid	Decrease HDACs activities	phase III clinical trial	solid tumors	[229]
Anacardic acid	Inhibit p300, PCAF and Tip60	Preclinical	Breast	[233]
Garcinol	Decrease HAT activities	Preclinical	Hepatocellular carcinoma	[237]
LTK14, LTK 15	Decrease HAT activities	Preclinical		[236]