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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 demethylating 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 aurointricarboxylic 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 acetyl-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 (ClinicalTrials.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 (ClinicalTrials.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 downregulation 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 tumorigenesis in TH-MYC 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 Zn²⁺ 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- κ B 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 ER α expression in ER α -negative breast cancer cells. EGCG is reported to remodel the chromatin structure of the ER α promoter leading to ER α 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 μ mol 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 μ M 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, 3 β -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; 3 β -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 pharmaceuticals, 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 RAR β 2 promoter. This histone acetylation induced expression of the peroxisome proliferator-activated receptor- γ (PPAR γ), 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

References

- Berger SL, Kouzarides T, Shiekhatair R, Shilatfard A. An operational definition of epigenetics. *Genes Dev.* 2009; 23(7):781–3. [PubMed: 19339683]
- Gal-Yam EN, Saito Y, Egger G, Jones PA. Cancer epigenetics: modifications, screening, and therapy. *Annu Rev Med.* 2008; 59:267–80. [PubMed: 17937590]
- Graff J I, Mansuy M. Epigenetic codes in cognition and behaviour. *Behav Brain Res.* 2008; 192(1): 70–87. [PubMed: 18353453]
- Wang GG, Allis CD, Chi P. Chromatin remodeling and cancer, Part II: ATP-dependent chromatin remodeling. *Trends Mol Med.* 2007; 13(9):373–80. [PubMed: 17822959]
- Wang GG, Allis CD, Chi P. Chromatin remodeling and cancer, Part I: Covalent histone modifications. *Trends Mol Med.* 2007; 13(9):363–72. [PubMed: 17822958]
- de Groote ML, Verschure PJ, Rots MG. Epigenetic Editing: targeted rewriting of epigenetic marks to modulate expression of selected target genes. *Nucleic Acids Res.* 2012; 40(21):10596–613. [PubMed: 23002135]
- Maunakea AK, Nagarajan RP, Bilenky M, Ballinger TJ, D'Souza C, Fouse SD, Johnson BE, Hong C, Nielsen C, Zhao Y, Turecki G, Delaney A, Varhol R, Thiessen N, Shchors K, Heine VM, Rowitch DH, Xing X, Fiore C, Schillebeeckx M, Jones SJ, Haussler D, Marra MA, Hirst M, Wang T, Costello JF. Conserved role of intragenic DNA methylation in regulating alternative promoters. *Nature.* 2010; 466(7303):253–7. [PubMed: 20613842]
- De Smet C, Lurquin C, Lethe B, Martelange V, Boon T. DNA methylation is the primary silencing mechanism for a set of germ line- and tumor-specific genes with a CpG-rich promoter. *Mol Cell Biol.* 1999; 19(11):7327–35. [PubMed: 10523621]
- Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. *Nat Rev Genet.* 2002; 3(6):415–28. [PubMed: 12042769]
- Baylin SB, Makos M, Wu JJ, Yen RW, de Bustros A, Vertino P, Nelkin BD. Abnormal patterns of DNA methylation in human neoplasia: potential consequences for tumor progression. *Cancer Cells.* 1991; 3(10):383–90. [PubMed: 1777359]
- Chen T, Li E. Establishment and maintenance of DNA methylation patterns in mammals. *Curr Top Microbiol Immunol.* 2006; 301:179–201. [PubMed: 16570848]
- Jones PL, Veenstra GJ, Wade PA, Vermaak D, Kass SU, Landsberger N, Strouboulis J, Wolffe AP. Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. *Nat Genet.* 1998; 19(2):187–91. [PubMed: 9620779]
- Bird A. DNA methylation patterns and epigenetic memory. *Genes Dev.* 2002; 16(1):6–21. [PubMed: 11782440]
- Tahiliani M, Koh KP, Shen Y, Pastor WA, Bandukwala H, Brudno Y, Agarwal S, Iyer LM, Liu DR, Aravind L, Rao A. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. *Science.* 2009; 324(5929):930–5. [PubMed: 19372391]

15. Ito S, D'Alessio AC, Taranova OV, Hong K, Sowers LC, Zhang Y. Role of Tet proteins in 5mC to 5hmC conversion, ES-cell self-renewal and inner cell mass specification. *Nature*. 2010; 466(7310): 1129–33. [PubMed: 20639862]
16. Kriaucionis S, Heintz N. The nuclear DNA base 5-hydroxymethylcytosine is present in Purkinje neurons and the brain. *Science*. 2009; 324(5929):929–30. [PubMed: 19372393]
17. Khorasanizadeh S. The nucleosome: from genomic organization to genomic regulation. *Cell*. 2004; 116(2):259–72. [PubMed: 14744436]
18. Dillon N. Gene regulation and large-scale chromatin organization in the nucleus. *Chromosome Res*. 2006; 14(1):117–26. [PubMed: 16506101]
19. Kouzarides T. Chromatin modifications and their function. *Cell*. 2007; 128(4):693–705. [PubMed: 17320507]
20. Tan M, Luo H, Lee S, Jin F, Yang JS, Montellier E, Buchou T, Cheng Z, Rousseaux S, Rajagopal N, Lu Z, Ye Z, Zhu Q, Wysocka J, Ye Y, Khochbin S, Ren B, Zhao Y. Identification of 67 histone marks and histone lysine crotonylation as a new type of histone modification. *Cell*. 2011; 146(6): 1016–28. [PubMed: 21925322]
21. Haberland M, Montgomery RL, Olson EN. The many roles of histone deacetylases in development and physiology: implications for disease and therapy. *Nat Rev Genet*. 2009; 10(1):32–42. [PubMed: 19065135]
22. Lan F, Bayliss PE, Rinn JL, Whetstone JR, Wang JK, Chen S, Iwase S, Alpatov R, Issaeva I, Canaani E, Roberts TM, Chang HY, Shi Y. A histone H3 lysine 27 demethylase regulates animal posterior development. *Nature*. 2007; 449(7163):689–94. [PubMed: 17851529]
23. Berlowitz L, Pallotta D. Acetylation of nuclear protein in the heterochromatin and euchromatin of mealy bugs. *Exp Cell Res*. 1972; 71(1):45–8. [PubMed: 5025943]
24. Luger K, Mader AW, Richmond RK, Sargent DF, Richmond TJ. Crystal structure of the nucleosome core particle at 2.8 Å resolution. *Nature*. 1997; 389(6648):251–60. [PubMed: 9305837]
25. Tremethick DJ. Higher-order structures of chromatin: the elusive 30 nm fiber. *Cell*. 2007; 128(4): 651–4. [PubMed: 17320503]
26. Barger JF, Nana-Sinkam SP. MicroRNA as tools and therapeutics in lung cancer. *Respir Med*. 2015
27. Luo C, Weber CE, Osen W, Bosserhoff AK, Eichmüller SB. The role of microRNAs in melanoma. *Eur J Cell Biol*. 2014; 93(1–2):11–22. [PubMed: 24602414]
28. Wang YL, Wu S, Jiang B, Yin FF, Zheng SS, Hou SC. Role of MicroRNAs in Prostate Cancer Pathogenesis. *Clin Genitourin Cancer*. 2015
29. Asangani IA, Harms PW, Dodson L, Pandhi M, Kunju LP, Maher CA, Fullen DR, Johnson TM, Giordano TJ, Palanisamy N, Chinnaiyan AM. Genetic and epigenetic loss of microRNA-31 leads to feed-forward expression of EZH2 in melanoma. *Oncotarget*. 2012; 3(9):1011–25. [PubMed: 22948084]
30. Taverna SD, Li H, Ruthenburg AJ, Allis CD, Patel DJ. How chromatin-binding modules interpret histone modifications: lessons from professional pocket pickers. *Nat Struct Mol Biol*. 2007; 14(11):1025–40. [PubMed: 17984965]
31. Chi P, Allis CD, Wang GG. Covalent histone modifications--miswritten, misinterpreted and mis-erased in human cancers. *Nat Rev Cancer*. 2010; 10(7):457–69. [PubMed: 20574448]
32. Lan F, Collins RE, De Cegli R, Alpatov R, Horton JR, Shi X, Gozani O, Cheng X, Shi Y. Recognition of unmethylated histone H3 lysine 4 links BHC80 to LSD1-mediated gene repression. *Nature*. 2007; 448(7154):718–22. [PubMed: 17687328]
33. Ooi SK, Qiu C, Bernstein E, Li K, Jia D, Yang Z, Erdjument-Bromage H, Tempst P, Lin SP, Allis CD, Cheng X, Bestor TH. DNMT3L connects unmethylated lysine 4 of histone H3 to de novo methylation of DNA. *Nature*. 2007; 448(7154):714–7. [PubMed: 17687327]
34. Jacobson RH, Ladurner AG, King DS, Tjian R. Structure and function of a human TAFII250 double bromodomain module. *Science*. 2000; 288(5470):1422–5. [PubMed: 10827952]
35. Gyuris A, Donovan DJ, Seymour KA, Lovasco LA, Smilowitz NR, Halperin AL, Klysik JE, Freiman RN. The chromatin-targeting protein Brd2 is required for neural tube closure and embryogenesis. *Biochim Biophys Acta*. 2009; 1789(5):413–21. [PubMed: 19362612]

36. Greenwald RJ, Tumang JR, Sinha A, Currier N, Cardiff RD, Rothstein TL, Faller DV, Denis GV. E mu-BRD2 transgenic mice develop B-cell lymphoma and leukemia. *Blood*. 2004; 103(4):1475–84. [PubMed: 14563639]
37. Filippakopoulos P, Qi J, Picaud S, Shen Y, Smith WB, Fedorov O, Morse EM, Keates T, Hickman TT, Felletar I, Philpott M, Munro S, McKeown MR, Wang Y, Christie AL, West N, Cameron MJ, Schwartz B, Heightman TD, La Thangue N, French CA, Wiest O, Kung AL, Knapp S, Bradner JE. Selective inhibition of BET bromodomains. *Nature*. 2010; 468(7327):1067–73. [PubMed: 20871596]
38. Dawson MA, Prinjha RK, Dittmann A, Giotopoulos G, Bantscheff M, Chan WI, Robson SC, Chung CW, Hopf C, Savitski MM, Huthmacher C, Gudgin E, Lugo D, Beinke S, Chapman TD, Roberts EJ, Soden PE, Auger KR, Mirguet O, Doehner K, Delwel R, Burnett AK, Jeffrey P, Drewes G, Lee K, Huntly BJ, Kouzarides T. Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. *Nature*. 2011; 478(7370):529–33. [PubMed: 21964340]
39. Nicodeme E, Jeffrey KL, Schaefer U, Beinke S, Dewell S, Chung CW, Chandwani R, Marazzi I, Wilson P, Coste H, White J, Kirilovsky J, Rice CM, Lora JM, Prinjha RK, Lee K, Tarakhovsky A. Suppression of inflammation by a synthetic histone mimic. *Nature*. 2010; 468(7327):1119–23. [PubMed: 21068722]
40. Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM, Kastiris E, Gilpatrick T, Paranal RM, Qi J, Chesi M, Schinzel AC, McKeown MR, Heffernan TP, Vakoc CR, Bergsagel PL, Ghobrial IM, Richardson PG, Young RA, Hahn WC, Anderson KC, Kung AL, Bradner JE, Mitsiades CS. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell*. 2011; 146(6):904–17. [PubMed: 21889194]
41. Mertz JA, Conery AR, Bryant BM, Sandy P, Balasubramanian S, Mele DA, Bergeron L, Sims RJ 3rd. Targeting MYC dependence in cancer by inhibiting BET bromodomains. *Proc Natl Acad Sci U S A*. 2011; 108(40):16669–74. [PubMed: 21949397]
42. Parry L, Clarke AR. The Roles of the Methyl-CpG Binding Proteins in Cancer. *Genes Cancer*. 2011; 2(6):618–30. [PubMed: 21941618]
43. Lopez-Serra L, Esteller M. Proteins that bind methylated DNA and human cancer: reading the wrong words. *Br J Cancer*. 2008; 98(12):1881–5. [PubMed: 18542062]
44. Muller I, Wischnewski F, Pantel K, Schwarzenbach H. Promoter- and cell-specific epigenetic regulation of CD44, Cyclin D2, GLIPR1 and PTEN by methyl-CpG binding proteins and histone modifications. *BMC Cancer*. 2010; 10:297. [PubMed: 20565761]
45. Wyhs N, Walker D, Giovino H, Yegnasubramanian S, Nelson WG. Time-Resolved Fluorescence Resonance Energy Transfer Assay for Discovery of Small-Molecule Inhibitors of Methyl-CpG Binding Domain Protein 2. *J Biomol Screen*. 2014; 19(7):1060–1069. [PubMed: 24608100]
46. Yang X, Lay F, Han H, Jones PA. Targeting DNA methylation for epigenetic therapy. *Trends Pharmacol Sci*. 2010; 31(11):536–46. [PubMed: 20846732]
47. Jones PA, Taylor SM. Cellular differentiation, cytidine analogs and DNA methylation. *Cell*. 1980; 20(1):85–93. [PubMed: 6156004]
48. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, Schoch R, Gattermann N, Sanz G, List A, Gore SD, Seymour JF, Bennett JM, Byrd J, Backstrom J, Zimmerman L, McKenzie D, Beach C, Silverman LR. International Vidaza High-Risk MDSSSG. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol*. 2009; 10(3):223–32. [PubMed: 19230772]
49. Tsai HC, Li H, Van Neste L, Cai Y, Robert C, Rassool FV, Shin JJ, Harbom KM, Beaty R, Pappou E, Harris J, Yen RW, Ahuja N, Brock MV, Stearns V, Feller-Kopman D, Yarmus LB, Lin YC, Welm AL, Issa JP, Minn I, Matsui W, Jang YY, Sharkis SJ, Baylin SB, Zahnow CA. Transient low doses of DNA-demethylating agents exert durable antitumor effects on hematological and epithelial tumor cells. *Cancer Cell*. 2012; 21(3):430–46. [PubMed: 22439938]
50. Ruiz-Carrillo A, Wangh LJ, Allfrey VG. Processing of newly synthesized histone molecules. *Science*. 1975; 190(4210):117–28. [PubMed: 1166303]

51. Lau OD, Kundu TK, Soccio RE, Ait-Si-Ali S, Khalil EM, Vassilev A, Wolffe AP, Nakatani Y, Roeder RG, Cole PA. HATs off: selective synthetic inhibitors of the histone acetyltransferases p300 and PCAF. *Mol Cell*. 2000; 5(3):589–95. [PubMed: 10882143]
52. Richon VM, Johnston D, Sneeringer CJ, Jin L, Majer CR, Elliston K, Jerva LF, Scott MP, Copeland RA. Chemogenetic analysis of human protein methyltransferases. *Chem Biol Drug Des*. 2011; 78(2):199–210. [PubMed: 21564555]
53. Daigle SR, Olhava EJ, Therkelsen CA, Majer CR, Sneeringer CJ, Song J, Johnston LD, Scott MP, Smith JJ, Xiao Y, Jin L, Kuntz KW, Chesworth R, Moyer MP, Bernt KM, Tseng JC, Kung AL, Armstrong SA, Copeland RA, Richon VM, Pollock RM. Selective killing of mixed lineage leukemia cells by a potent small-molecule DOT1L inhibitor. *Cancer Cell*. 2011; 20(1):53–65. [PubMed: 21741596]
54. Daigle SR, Olhava EJ, Therkelsen CA, Basavapathruni A, Jin L, Boriack-Sjodin PA, Allain CJ, Klaus CR, Raimondi A, Scott MP, Waters NJ, Chesworth R, Moyer MP, Copeland RA, Richon VM, Pollock RM. Potent inhibition of DOT1L as treatment of MLL-fusion leukemia. *Blood*. 2013; 122(6):1017–25. [PubMed: 23801631]
55. Morey L, Helin K. Polycomb group protein-mediated repression of transcription. *Trends Biochem Sci*. 2010; 35(6):323–32. [PubMed: 20346678]
56. Varambally S, Dhanasekaran SM, Zhou M, Barrette TR, Kumar-Sinha C, Sanda MG, Ghosh D, Pienta KJ, Sewalt RG, Otte AP, Rubin MA, Chinnaiyan AM. The polycomb group protein EZH2 is involved in progression of prostate cancer. *Nature*. 2002; 419(6907):624–9. [PubMed: 12374981]
57. Kleer CG, Cao Q, Varambally S, Shen R, Ota I, Tomlins SA, Ghosh D, Sewalt RG, Otte AP, Hayes DF, Sabel MS, Livant D, Weiss SJ, Rubin MA, Chinnaiyan AM. EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells. *Proc Natl Acad Sci U S A*. 2003; 100(20):11606–11. [PubMed: 14500907]
58. Wagener N, Macher-Goeppinger S, Pritsch M, Husing J, Hoppe-Seyler K, Schirmacher P, Pfitzenmaier J, Haferkamp A, Hoppe-Seyler F, Hohenfellner M. Enhancer of zeste homolog 2 (EZH2) expression is an independent prognostic factor in renal cell carcinoma. *BMC Cancer*. 2010; 10:524. [PubMed: 20920340]
59. Takawa M, Masuda K, Kunizaki M, Daigo Y, Takagi K, Iwai Y, Cho HS, Toyokawa G, Yamane Y, Maejima K, Field HI, Kobayashi T, Akasu T, Sugiyama M, Tsuchiya E, Atomi Y, Ponder BA, Nakamura Y, Hamamoto R. Validation of the histone methyltransferase EZH2 as a therapeutic target for various types of human cancer and as a prognostic marker. *Cancer Sci*. 2011; 102(7):1298–305. [PubMed: 21539681]
60. Tan J, Yang X, Zhuang L, Jiang X, Chen W, Lee PL, Karuturi RK, Tan PB, Liu ET, Yu Q. Pharmacologic disruption of Polycomb-repressive complex 2-mediated gene repression selectively induces apoptosis in cancer cells. *Genes Dev*. 2007; 21(9):1050–63. [PubMed: 17437993]
61. Miranda TB, Cortez CC, Yoo CB, Liang G, Abe M, Kelly TK, Marquez VE, Jones PA. DZNep is a global histone methylation inhibitor that reactivates developmental genes not silenced by DNA methylation. *Mol Cancer Ther*. 2009; 8(6):1579–88. [PubMed: 19509260]
62. Knutson SK, Wigle TJ, Warholc NM, Sneeringer CJ, Allain CJ, Klaus CR, Sacks JD, Raimondi A, Majer CR, Song J, Scott MP, Jin L, Smith JJ, Olhava EJ, Chesworth R, Moyer MP, Richon VM, Copeland RA, Keilhack H, Pollock RM, Kuntz KW. A selective inhibitor of EZH2 blocks H3K27 methylation and kills mutant lymphoma cells. *Nat Chem Biol*. 2012; 8(11):890–6. [PubMed: 23023262]
63. McCabe MT, Ott HM, Ganji G, Korenchuk S, Thompson C, Van Aller GS, Liu Y, Graves AP, Della Pietra A 3rd, Diaz E, LaFrance LV, Mellinger M, Duquenne C, Tian X, Kruger RG, McHugh CF, Brandt M, Miller WH, Dhanak D, Verma SK, Tummino PJ, Creasy CL. EZH2 inhibition as a therapeutic strategy for lymphoma with EZH2-activating mutations. *Nature*. 2012; 492(7427):108–12. [PubMed: 23051747]
64. Qi W, Chan H, Teng L, Li L, Chuai S, Zhang R, Zeng J, Li M, Fan H, Lin Y, Gu J, Ardayfio O, Zhang JH, Yan X, Fang J, Mi Y, Zhang M, Zhou T, Feng G, Chen Z, Li G, Yang T, Zhao K, Liu X, Yu Z, Lu CX, Atadja P, Li E. Selective inhibition of Ezh2 by a small molecule inhibitor blocks tumor cells proliferation. *Proc Natl Acad Sci U S A*. 2012; 109(52):21360–5. [PubMed: 23236167]

65. Knutson SK, Warholik NM, Wigle TJ, Klaus CR, Allain CJ, Raimondi A, Porter Scott M, Chesworth R, Moyer MP, Copeland RA, Richon VM, Pollock RM, Kuntz KW, Keilhack H. Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. *Proc Natl Acad Sci U S A*. 2013; 110(19):7922–7. [PubMed: 23620515]
66. Scourzac L, Mouly E, Bernard OA. TET proteins and the control of cytosine demethylation in cancer. *Genome Med*. 2015; 7(1):9. [PubMed: 25632305]
67. Lian CG, Xu Y, Ceol C, Wu F, Larson A, Dresser K, Xu W, Tan L, Hu Y, Zhan Q, Lee CW, Hu D, Lian BQ, Kleffel S, Yang Y, Neiswender J, Khorasani AJ, Fang R, Lezcano C, Duncan LM, Scolyer RA, Thompson JF, Kakavand H, Houvras Y, Zon LI, Mihm MC Jr, Kaiser UB, Schatton T, Woda BA, Murphy GF, Shi YG. Loss of 5-hydroxymethylcytosine is an epigenetic hallmark of melanoma. *Cell*. 2012; 150(6):1135–46. [PubMed: 22980977]
68. Stransky N, Egloff AM, Tward AD, Kostic AD, Cibulskis K, Sivachenko A, Kryukov GV, Lawrence MS, Sougnez C, McKenna A, Shefler E, Ramos AH, Stojanov P, Carter SL, Voet D, Cortes ML, Auclair D, Berger MF, Saksena G, Guiducci C, Onofrio RC, Parkin M, Romkes M, Weissfeld JL, Seethala RR, Wang L, Rangel-Escareno C, Fernandez-Lopez JC, Hidalgo-Miranda A, Melendez-Zajgla J, Winckler W, Ardlie K, Gabriel SB, Meyerson M, Lander ES, Getz G, Golub TR, Garraway LA, Grandis JR. The mutational landscape of head and neck squamous cell carcinoma. *Science*. 2011; 333(6046):1157–60. [PubMed: 21798893]
69. Kan Z, Jaiswal BS, Stinson J, Janakiraman V, Bhatt D, Stern HM, Yue P, Haverty PM, Bourgon R, Zheng J, Moorhead M, Chaudhuri S, Tomsho LP, Peters BA, Pujara K, Cordes S, Davis DP, Carlton VE, Yuan W, Li L, Wang W, Eigenbrot C, Kaminker JS, Eberhard DA, Waring P, Schuster SC, Modrusan Z, Zhang Z, Stokoe D, de Sauvage FJ, Faham M, Seshagiri S. Diverse somatic mutation patterns and pathway alterations in human cancers. *Nature*. 2010; 466(7308):869–73. [PubMed: 20668451]
70. Barth TK, Imhof A. Fast signals and slow marks: the dynamics of histone modifications. *Trends Biochem Sci*. 2010; 35(11):618–26. [PubMed: 20685123]
71. Zee BM, Levin RS, Xu B, LeRoy G, Wingreen NS, Garcia BA. In vivo residue-specific histone methylation dynamics. *J Biol Chem*. 2010; 285(5):3341–50. [PubMed: 19940157]
72. Shi Y, Lan F, Matson C, Mulligan P, Whetstine JR, Cole PA, Casero RA, Shi Y. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell*. 2004; 119(7):941–53. [PubMed: 15620353]
73. Tsukada Y, Fang J, Erdjument-Bromage H, Warren ME, Borchers CH, Tempst P, Zhang Y. Histone demethylation by a family of JmjC domain-containing proteins. *Nature*. 2006; 439(7078):811–6. [PubMed: 16362057]
74. Whetstine JR, Nottke A, Lan F, Huarte M, Smolikov S, Chen Z, Spooner E, Li E, Zhang G, Colaiacovo M, Shi Y. Reversal of histone lysine trimethylation by the JMJD2 family of histone demethylases. *Cell*. 2006; 125(3):467–81. [PubMed: 16603238]
75. Fitzpatrick PF. Oxidation of amines by flavoproteins. *Arch Biochem Biophys*. 2010; 493(1):13–25. [PubMed: 19651103]
76. Kahl P, Gullotti L, Heukamp LC, Wolf S, Friedrichs N, Vorreuther R, Solleder G, Bastian PJ, Ellinger J, Metzger E, Schule R, Buettner R. Androgen receptor coactivators lysine-specific histone demethylase 1 and four and a half LIM domain protein 2 predict risk of prostate cancer recurrence. *Cancer Res*. 2006; 66(23):11341–7. [PubMed: 17145880]
77. Hayami S, Kelly JD, Cho HS, Yoshimatsu M, Unoki M, Tsunoda T, Field HI, Neal DE, Yamaue H, Ponder BA, Nakamura Y, Hamamoto R. Overexpression of LSD1 contributes to human carcinogenesis through chromatin regulation in various cancers. *Int J Cancer*. 2011; 128(3):574–86. [PubMed: 20333681]
78. Kauffman EC, Robinson BD, Downes MJ, Powell LG, Lee MM, Scherr DS, Gudas LJ, Mongan NP. Role of androgen receptor and associated lysine-demethylase coregulators, LSD1 and JMJD2A, in localized and advanced human bladder cancer. *Mol Carcinog*. 2011; 50(12):931–44. [PubMed: 21400613]
79. Lee MG, Wynder C, Schmidt DM, McCafferty DG, Shiekhhattar R. Histone H3 lysine 4 demethylation is a target of nonselective antidepressive medications. *Chem Biol*. 2006; 13(6):563–7. [PubMed: 16793513]

80. Schenk T, Chen WC, Gollner S, Howell L, Jin L, Hebestreit K, Klein HU, Popescu AC, Burnett A, Mills K, Casero RA Jr, Marton L, Woster P, Minden MD, Dugas M, Wang JC, Dick JE, Muller-Tidow C, Petrie K, Zelent A. Inhibition of the LSD1 (KDM1A) demethylase reactivates the all-trans-retinoic acid differentiation pathway in acute myeloid leukemia. *Nat Med*. 2012; 18(4):605–11. [PubMed: 22406747]
81. Willmann D, Lim S, Wetzel S, Metzger E, Jandausch A, Wilk W, Jung M, Forne I, Imhof A, Janzer A, Kirfel J, Waldmann H, Schule R, Buettner R. Impairment of prostate cancer cell growth by a selective and reversible lysine-specific demethylase 1 inhibitor. *Int J Cancer*. 2012; 131(11):2704–9. [PubMed: 22447389]
82. Cloos PA, Christensen J, Agger K, Maiolica A, Rappsilber J, Antal T, Hansen KH, Helin K. The putative oncogene GASC1 demethylates tri- and dimethylated lysine 9 on histone H3. *Nature*. 2006; 442(7100):307–11. [PubMed: 16732293]
83. Kruidenier L, Chung CW, Cheng Z, Liddle J, Che K, Joberty G, Bantscheff M, Bountra C, Bridges A, Diallo H, Eberhard D, Hutchinson S, Jones E, Katso R, Leveridge M, Mander PK, Mosley J, Ramirez-Molina C, Rowland P, Schofield CJ, Sheppard RJ, Smith JE, Swales C, Tanner R, Thomas P, Tumber A, Drewes G, Oppermann U, Patel DJ, Lee K, Wilson DM. A selective jumonji H3K27 demethylase inhibitor modulates the proinflammatory macrophage response. *Nature*. 2012; 488(7411):404–8. [PubMed: 22842901]
84. Haigis MC, Sinclair DA. Mammalian sirtuins: biological insights and disease relevance. *Annu Rev Pathol*. 2010; 5:253–95. [PubMed: 20078221]
85. Hu J, Jing H, Lin H. Sirtuin inhibitors as anticancer agents. *Future Med Chem*. 2014; 6(8):945–66. [PubMed: 24962284]
86. Hu J, He B, Bhargava S, Lin H. A fluorogenic assay for screening Sirt6 modulators. *Org Biomol Chem*. 2013; 11(32):5213–6. [PubMed: 23839075]
87. Tervo AJ, Kyrylenko S, Niskanen P, Salminen A, Leppanen J, Nyronen TH, Jarvinen T, Poso A. An in silico approach to discovering novel inhibitors of human sirtuin type 2. *J Med Chem*. 2004; 47(25):6292–8. [PubMed: 15566299]
88. Audrito V, Vaisitti T, Rossi D, Gottardi D, D'Arena G, Laurenti L, Gaidano G, Malavasi F, Deaglio S. Nicotinamide blocks proliferation and induces apoptosis of chronic lymphocytic leukemia cells through activation of the p53/miR-34a/SIRT1 tumor suppressor network. *Cancer Res*. 2011; 71(13):4473–83. [PubMed: 21565980]
89. Jung-Hynes B, Nihal M, Zhong W, Ahmad N. Role of sirtuin histone deacetylase SIRT1 in prostate cancer. A target for prostate cancer management via its inhibition? *J Biol Chem*. 2009; 284(6):3823–32. [PubMed: 19075016]
90. Yuan J, Minter-Dykhouse K, Lou Z. A c-Myc-SIRT1 feedback loop regulates cell growth and transformation. *J Cell Biol*. 2009; 185(2):203–11. [PubMed: 19364925]
91. Luo J, Su F, Chen D, Shiloh A, Gu W. Deacetylation of p53 modulates its effect on cell growth and apoptosis. *Nature*. 2000; 408(6810):377–81. [PubMed: 11099047]
92. Ropero S, Esteller M. The role of histone deacetylases (HDACs) in human cancer. *Mol Oncol*. 2007; 1(1):19–25. [PubMed: 19383284]
93. West AC, Smyth MJ, Johnstone RW. The anticancer effects of HDAC inhibitors require the immune system. *Oncoimmunology*. 2014; 3(1):e27414. [PubMed: 24701376]
94. West AC, Johnstone RW. New and emerging HDAC inhibitors for cancer treatment. *J Clin Invest*. 2014; 124(1):30–9. [PubMed: 24382387]
95. Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. *Nat Rev Drug Discov*. 2006; 5(9):769–84. [PubMed: 16955068]
96. Nebbioso A, Clarke N, Voltz E, Germain E, Ambrosino C, Bontempo P, Alvarez R, Schiavone EM, Ferrara F, Bresciani F, Weisz A, de Lera AR, Gronemeyer H, Altucci L. Tumor-selective action of HDAC inhibitors involves TRAIL induction in acute myeloid leukemia cells. *Nat Med*. 2005; 11(1):77–84. [PubMed: 15619633]
97. Geng L, Cuneo KC, Fu A, Tu T, Atadja PW, Hallahan DE. Histone deacetylase (HDAC) inhibitor LBH589 increases duration of gamma-H2AX foci and confines HDAC4 to the cytoplasm in irradiated non-small cell lung cancer. *Cancer Res*. 2006; 66(23):11298–304. [PubMed: 17145876]

98. Qian DZ, Kato Y, Shabbeer S, Wei Y, Verheul HM, Salumbides B, Sanni T, Atadja P, Pili R. Targeting tumor angiogenesis with histone deacetylase inhibitors: the hydroxamic acid derivative LBH589. *Clin Cancer Res*. 2006; 12(2):634–42. [PubMed: 16428510]
99. Piekarz RL, Frye R, Turner M, Wright JJ, Allen SL, Kirschbaum MH, Zain J, Prince HM, Leonard JP, Geskin LJ, Reeder C, Joske D, Figg WD, Gardner ER, Steinberg SM, Jaffe ES, Stetler-Stevenson M, Lade S, Fojo AT, Bates SE. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *J Clin Oncol*. 2009; 27(32):5410–7. [PubMed: 19826128]
100. Whittaker SJ, Demierre MF, Kim EJ, Rook AH, Lerner A, Duvic M, Scarisbrick J, Reddy S, Robak T, Becker JC, Samtsov A, McCulloch W, Kim YH. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2010; 28(29):4485–91. [PubMed: 20697094]
101. Piekarz RL, Frye R, Prince HM, Kirschbaum MH, Zain J, Allen SL, Jaffe ES, Ling A, Turner M, Peer CJ, Figg WD, Steinberg SM, Smith S, Joske D, Lewis I, Hutchins L, Craig M, Fojo AT, Wright JJ, Bates SE. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. *Blood*. 2011; 117(22):5827–34. [PubMed: 21355097]
102. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, Caballero D, Borchmann P, Morschhauser F, Wilhelm M, Pinter-Brown L, Padmanabhan S, Shustov A, Nichols J, Carroll S, Balser J, Balser B, Horwitz S. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol*. 2012; 30(6):631–6. [PubMed: 22271479]
103. Vickers CJ, Olsen CA, Leman LJ, Ghadiri MR. Discovery of HDAC Inhibitors That Lack an Active Site Zn(2+)-Binding Functional Group. *ACS Med Chem Lett*. 2012; 3(6):505–8. [PubMed: 24900500]
104. Yoshida K, Yamaguchi K, Mizuno A, Unno Y, Asai A, Sone T, Yokosawa H, Matsuda A, Arisawa M, Shuto S. Three-dimensional structure-activity relationship study of belactosin A and its stereo- and regioisomers: development of potent proteasome inhibitors by a stereochemical diversity-oriented strategy. *Org Biomol Chem*. 2009; 7(9):1868–77. [PubMed: 19590782]
105. Hu J, Colburn NH. Histone deacetylase inhibition down-regulates cyclin D1 transcription by inhibiting nuclear factor-kappaB/p65 DNA binding. *Mol Cancer Res*. 2005; 3(2):100–9. [PubMed: 15755876]
106. Chan ST, Yang NC, Huang CS, Liao JW, Yeh SL. Quercetin enhances the antitumor activity of trichostatin A through upregulation of p53 protein expression in vitro and in vivo. *PLoS One*. 2013; 8(1):e54255. [PubMed: 23342112]
107. Mann BS, Johnson JR, Cohen MH, Justice R, Pazdur R. FDA approval summary: vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. *Oncologist*. 2007; 12(10):1247–52. [PubMed: 17962618]
108. Marks PA. Discovery and development of SAHA as an anticancer agent. *Oncogene*. 2007; 26(9):1351–6. [PubMed: 17322921]
109. Lee HZ, Kwitkowski VE, Del Valle PL, Ricci MS, Saber H, Habtemariam BA, Bullock J, Bloomquist E, Shen YL, Chen XH, Brown J, Mehrotra N, Dorff S, Charlab R, Kane RC, Kaminskas E, Justice R, Farrell AT, Pazdur R. FDA Approval: Belinostat for the Treatment of Patients with Relapsed or Refractory Peripheral T-cell Lymphoma. *Clin Cancer Res*. 2015
110. Garnock-Jones KP. Panobinostat: first global approval. *Drugs*. 2015; 75(6):695–704. [PubMed: 25837990]
111. Surh YJ. Cancer chemoprevention with dietary phytochemicals. *Nat Rev Cancer*. 2003; 3(10):768–80. [PubMed: 14570043]
112. Kumar B, Yadav A, Hideg K, Kuppusamy P, Teknos TN, Kumar P. A novel curcumin analog (H-4073) enhances the therapeutic efficacy of cisplatin treatment in head and neck cancer. *PLoS One*. 2014; 9(3):e93208. [PubMed: 24675768]
113. Malhotra A, Nair P, Dhawan DK. Study to evaluate molecular mechanics behind synergistic chemo-preventive effects of curcumin and resveratrol during lung carcinogenesis. *PLoS One*. 2014; 9(4):e93820. [PubMed: 24705375]

114. Guo Y, Shu L, Zhang C, Su ZY, Kong AN. Curcumin inhibits anchorage-independent growth of HT29 human colon cancer cells by targeting epigenetic restoration of the tumor suppressor gene DLEC1. *Biochem Pharmacol.* 2015
115. Sarkar R, Mukherjee A, Mukherjee S, Biswas R, Biswas J, Roy M. Curcumin augments the efficacy of antitumor drugs used in leukemia by modulation of heat shock proteins via HDAC6. *J Environ Pathol Toxicol Oncol.* 2014; 33(3):247–63. [PubMed: 25272063]
116. Balasubramanyam K, Varier RA, Altaf M, Swaminathan V, Siddappa NB, Ranga U, Kundu TK. Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. *J Biol Chem.* 2004; 279(49):51163–71. [PubMed: 15383533]
117. Kang J, Chen J, Shi Y, Jia J, Zhang Y. Curcumin-induced histone hypoacetylation: the role of reactive oxygen species. *Biochem Pharmacol.* 2005; 69(8):1205–13. [PubMed: 15794941]
118. Connors SK, Chornokur G, Kumar NB. New insights into the mechanisms of green tea catechins in the chemoprevention of prostate cancer. *Nutr Cancer.* 2012; 64(1):4–22. [PubMed: 22098273]
119. Chung MY, Lim TG, Lee KW. Molecular mechanisms of chemopreventive phytochemicals against gastroenterological cancer development. *World J Gastroenterol.* 2013; 19(7):984–93. [PubMed: 23467658]
120. Thakur VS, Gupta K, Gupta S. Green tea polyphenols increase p53 transcriptional activity and acetylation by suppressing class I histone deacetylases. *Int J Oncol.* 2012; 41(1):353–61. [PubMed: 22552582]
121. Thakur VS, Gupta K, Gupta S. Green tea polyphenols causes cell cycle arrest and apoptosis in prostate cancer cells by suppressing class I histone deacetylases. *Carcinogenesis.* 2012; 33(2): 377–84. [PubMed: 22114073]
122. Choi KC, Jung MG, Lee YH, Yoon JC, Kwon SH, Kang HB, Kim MJ, Cha JH, Kim YJ, Jun WJ, Lee JM, Yoon HG. Epigallocatechin-3-gallate, a histone acetyltransferase inhibitor, inhibits EBV-induced B lymphocyte transformation via suppression of RelA acetylation. *Cancer Res.* 2009; 69(2):583–92. [PubMed: 19147572]
123. Nandakumar V, Vaid M, Katiyar SK. (–)-Epigallocatechin-3-gallate reactivates silenced tumor suppressor genes, Cip1/p21 and p16INK4a, by reducing DNA methylation and increasing histones acetylation in human skin cancer cells. *Carcinogenesis.* 2011; 32(4):537–44. [PubMed: 21209038]
124. Li Y, Yuan YY, Meeran SM, Tollefsbol TO. Synergistic epigenetic reactivation of estrogen receptor-alpha (ERalpha) by combined green tea polyphenol and histone deacetylase inhibitor in ERalpha-negative breast cancer cells. *Mol Cancer.* 2010; 9:274. [PubMed: 20946668]
125. Zhang Y, Wang X, Han L, Zhou Y, Sun S. Green tea polyphenol EGCG reverse cisplatin resistance of A549/DDP cell line through candidate genes demethylation. *Biomed Pharmacother.* 2015; 69:285–90. [PubMed: 25661371]
126. Khan MA, Hussain A, Sundaram MK, Alalami U, Gunasekera D, Ramesh L, Hamza A, Quraishi U. (–)-Epigallocatechin-3-gallate reverses the expression of various tumor-suppressor genes by inhibiting DNA methyltransferases and histone deacetylases in human cervical cancer cells. *Oncol Rep.* 2015; 33(4):1976–84. [PubMed: 25682960]
127. Balasubramanian S, Adhikary G, Eckert RL. The Bmi-1 polycomb protein antagonizes the (–)-epigallocatechin-3-gallate-dependent suppression of skin cancer cell survival. *Carcinogenesis.* 2010; 31(3):496–503. [PubMed: 20015867]
128. Choudhury SR, Balasubramanian S, Chew YC, Han B, Marquez VE, Eckert RL. (–)-Epigallocatechin-3-gallate and DZNep reduce polycomb protein level via a proteasome-dependent mechanism in skin cancer cells. *Carcinogenesis.* 2011; 32(10):1525–32. [PubMed: 21798853]
129. Deb G, Thakur VS, Limaye AM, Gupta S. Epigenetic induction of tissue inhibitor of matrix metalloproteinase-3 by green tea polyphenols in breast cancer cells. *Mol Carcinog.* 2015; 54(6): 485–99. [PubMed: 24481780]
130. Balasubramanian S, Scharadin TM, Han B, Xu W, Eckert RL. The Bmi-1 helix-turn and ring finger domains are required for Bmi-1 antagonism of (–) epigallocatechin-3-gallate suppression of skin cancer cell survival. *Cell Signal.* 2015; 27(7):1336–1344. [PubMed: 25843776]

131. Basak S, Pookot D, Noonan EJ, Dahiya R. Genistein down-regulates androgen receptor by modulating HDAC6-Hsp90 chaperone function. *Mol Cancer Ther.* 2008; 7(10):3195–202. [PubMed: 18852123]
132. Ruiz PA, Braune A, Holzlwimmer G, Quintanilla-Fend L, Haller D. Quercetin inhibits TNF-induced NF-kappaB transcription factor recruitment to proinflammatory gene promoters in murine intestinal epithelial cells. *J Nutr.* 2007; 137(5):1208–15. [PubMed: 17449583]
133. Priyadarsini RV, Vinothini G, Murugan RS, Manikandan P, Nagini S. The flavonoid quercetin modulates the hallmark capabilities of hamster buccal pouch tumors. *Nutr Cancer.* 2011; 63(2): 218–26. [PubMed: 21294050]
134. Roy SK, Chen Q, Fu J, Shankar S, Srivastava RK. Resveratrol inhibits growth of orthotopic pancreatic tumors through activation of FOXO transcription factors. *PLoS One.* 2011; 6(9):e25166. [PubMed: 21980390]
135. Yang Q, Wang B, Zang W, Wang X, Liu Z, Li W, Jia J. Resveratrol inhibits the growth of gastric cancer by inducing G1 phase arrest and senescence in a Sirt1-dependent manner. *PLoS One.* 2013; 8(11):e70627. [PubMed: 24278101]
136. Venturelli S, Berger A, Bocker A, Busch C, Weiland T, Noor S, Leischner C, Schleicher S, Mayer M, Weiss TS, Bischoff SC, Lauer UM, Bitzer M. Resveratrol as a pan-HDAC inhibitor alters the acetylation status of histone [corrected] proteins in human-derived hepatoblastoma cells. *PLoS One.* 2013; 8(8):e73097. [PubMed: 24023672]
137. Dhar S, Kumar A, Li K, Tzivion G, Levenson AS. Resveratrol regulates PTEN/Akt pathway through inhibition of MTA1/HDAC unit of the NuRD complex in prostate cancer. *Biochim Biophys Acta.* 2015; 1853(2):265–75. [PubMed: 25447541]
138. Schneider-Stock R, Ghantous A, Bajbouj K, Saikali M, Darwiche N. Epigenetic mechanisms of plant-derived anticancer drugs. *Front Biosci (Landmark Ed).* 2012; 17:129–73. [PubMed: 22201736]
139. Hsu A, Wong CP, Yu Z, Williams DE, Dashwood RH, Ho E. Promoter de-methylation of cyclin D2 by sulforaphane in prostate cancer cells. *Clin Epigenetics.* 2011; 3:3. [PubMed: 22303414]
140. Su ZY, Zhang C, Lee JH, Shu L, Wu TY, Khor TO, Conney AH, Lu YP, Kong AN. Requirement and epigenetics reprogramming of Nrf2 in suppression of tumor promoter TPA-induced mouse skin cell transformation by sulforaphane. *Cancer Prev Res (Phila).* 2014; 7(3):319–29. [PubMed: 24441674]
141. Tortorella SM, Royce SG, Licciardi PV, Karagiannis TC. Dietary Sulforaphane in Cancer Chemoprevention: The Role of Epigenetic Regulation and HDAC Inhibition. *Antioxid Redox Signal.* 2014
142. Li Q, Eades G, Yao Y, Zhang Y, Zhou Q. Characterization of a stem-like subpopulation in basal-like ductal carcinoma in situ (DCIS) lesions. *J Biol Chem.* 2014; 289(3):1303–12. [PubMed: 24297178]
143. Cang S, Ma Y, Chiao JW, Liu D. Phenethyl isothiocyanate and paclitaxel synergistically enhanced apoptosis and alpha-tubulin hyperacetylation in breast cancer cells. *Exp Hematol Oncol.* 2014; 3(1):5. [PubMed: 24495785]
144. Liu K, Cang S, Ma Y, Chiao JW. Synergistic effect of paclitaxel and epigenetic agent phenethyl isothiocyanate on growth inhibition, cell cycle arrest and apoptosis in breast cancer cells. *Cancer Cell Int.* 2013; 13(1):10. [PubMed: 23388416]
145. Wang LG, Chiao JW. Prostate cancer chemopreventive activity of phenethyl isothiocyanate through epigenetic regulation (review). *Int J Oncol.* 2010; 37(3):533–9. [PubMed: 20664922]
146. Druesne-Pecollo N, Latino-Martel P. Modulation of histone acetylation by garlic sulfur compounds. *Anticancer Agents Med Chem.* 2011; 11(3):254–9. [PubMed: 21269249]
147. Lee JH, Kim KA, Kwon KB, Kim EK, Lee YR, Song MY, Koo JH, Ka SO, Park JW, Park BH. Diallyl disulfide accelerates adipogenesis in 3T3-L1 cells. *Int J Mol Med.* 2007; 20(1):59–64. [PubMed: 17549389]
148. Fimognari C, Lenzi M, Hrelia P. Chemoprevention of cancer by isothiocyanates and anthocyanins: mechanisms of action and structure-activity relationship. *Curr Med Chem.* 2008; 15(5):440–7. [PubMed: 18288999]

149. Ho E, Clarke JD, Dashwood RH. Dietary sulforaphane, a histone deacetylase inhibitor for cancer prevention. *J Nutr*. 2009; 139(12):2393–6. [PubMed: 19812222]
150. Dashwood RH, Ho E. Dietary agents as histone deacetylase inhibitors: sulforaphane and structurally related isothiocyanates. *Nutr Rev*. 2008; 66(Suppl 1):S36–8. [PubMed: 18673487]
151. Telang U, Brazeau DA, Morris ME. Comparison of the effects of phenethyl isothiocyanate and sulforaphane on gene expression in breast cancer and normal mammary epithelial cells. *Exp Biol Med* (Maywood). 2009; 234(3):287–95. [PubMed: 19144873]
152. Myzak MC, Karplus PA, Chung FL, Dashwood RH. A novel mechanism of chemoprotection by sulforaphane: inhibition of histone deacetylase. *Cancer Res*. 2004; 64(16):5767–74. [PubMed: 15313918]
153. Myzak MC, Tong P, Dashwood WM, Dashwood RH, Ho E. Sulforaphane retards the growth of human PC-3 xenografts and inhibits HDAC activity in human subjects. *Exp Biol Med* (Maywood). 2007; 232(2):227–34. [PubMed: 17259330]
154. Meeran SM, Patel SN, Tollefsbol TO. Sulforaphane causes epigenetic repression of hTERT expression in human breast cancer cell lines. *PLoS One*. 2010; 5(7):e11457. [PubMed: 20625516]
155. Fan H, Zhang R, Tesfaye D, Tholen E, Looft C, Holker M, Schellander K, Cinar MU. Sulforaphane causes a major epigenetic repression of myostatin in porcine satellite cells. *Epigenetics*. 2012; 7(12):1379–90. [PubMed: 23092945]
156. Kar S, Sengupta D, Deb M, Shilpi A, Parbin S, Rath SK, Pradhan N, Rakshit M, Patra SK. Expression profiling of DNA methylation-mediated epigenetic gene-silencing factors in breast cancer. *Clin Epigenetics*. 2014; 6(1):20. [PubMed: 25478034]
157. Gerhauser C. Epigenetic impact of dietary isothiocyanates in cancer chemoprevention. *Curr Opin Clin Nutr Metab Care*. 2013; 16(4):405–10. [PubMed: 23657153]
158. Chorley BN, Campbell MR, Wang X, Karaca M, Sambandan D, Bangura F, Xue P, Pi J, Kleeberger SR, Bell DA. Identification of novel NRF2-regulated genes by ChIP-Seq: influence on retinoid X receptor alpha. *Nucleic Acids Res*. 2012; 40(15):7416–29. [PubMed: 22581777]
159. Wang LG, Liu XM, Fang Y, Dai W, Chiao FB, Puccio GM, Feng J, Liu D, Chiao JW. De-repression of the p21 promoter in prostate cancer cells by an isothiocyanate via inhibition of HDACs and c-Myc. *Int J Oncol*. 2008; 33(2):375–80. [PubMed: 18636159]
160. Wang LG, Beklemisheva A, Liu XM, Ferrari AC, Feng J, Chiao JW. Dual action on promoter demethylation and chromatin by an isothiocyanate restored GSTP1 silenced in prostate cancer. *Mol Carcinog*. 2007; 46(1):24–31. [PubMed: 16921492]
161. Finnin MS, Donigian JR, Cohen A, Richon VM, Rifkind RA, Marks PA, Breslow R, Pavletich NP. Structures of a histone deacetylase homologue bound to the TSA and SAHA inhibitors. *Nature*. 1999; 401(6749):188–93. [PubMed: 10490031]
162. Guyonnet D, Berges R, Siess MH, Pinnert MF, Chagnon MC, Suschetet M, Le Bon AM. Post-initiation modulating effects of allyl sulfides in rat hepatocarcinogenesis. *Food Chem Toxicol*. 2004; 42(9):1479–85. [PubMed: 15234078]
163. Nian H, Delage B, Ho E, Dashwood RH. Modulation of histone deacetylase activity by dietary isothiocyanates and allyl sulfides: studies with sulforaphane and garlic organosulfur compounds. *Environ Mol Mutagen*. 2009; 50(3):213–21. [PubMed: 19197985]
164. Lea MA, Randolph VM, Patel M. Increased acetylation of histones induced by diallyl disulfide and structurally related molecules. *Int J Oncol*. 1999; 15(2):347–52. [PubMed: 10402246]
165. Nian H, Delage B, Pinto JT, Dashwood RH. Allyl mercaptan, a garlic-derived organosulfur compound, inhibits histone deacetylase and enhances Sp3 binding on the P21WAF1 promoter. *Carcinogenesis*. 2008; 29(9):1816–24. [PubMed: 18628250]
166. Druesne-Pecollo N, Chaumontet C, Latino-Martel P. Diallyl disulfide increases histone acetylation in colon cells in vitro and in vivo. *Nutr Rev*. 2008; 66(Suppl 1):S39–41. [PubMed: 18673488]
167. Druesne N, Pagniez A, Mayeur C, Thomas M, Cherbuy C, Duee PH, Martel P, Chaumontet C. Diallyl disulfide (DADS) increases histone acetylation and p21(waf1/cip1) expression in human colon tumor cell lines. *Carcinogenesis*. 2004; 25(7):1227–36. [PubMed: 14976134]

168. Druesne-Pecollo N, Chaumontet C, Pagniez A, Vaugelade P, Bruneau A, Thomas M, Cherbuy C, Duee PH, Martel P. In vivo treatment by diallyl disulfide increases histone acetylation in rat colonocytes. *Biochem Biophys Res Commun*. 2007; 354(1):140–7. [PubMed: 17210128]
169. Bishayee A, Ahmed S, Brankov N, Perloff M. Triterpenoids as potential agents for the chemoprevention and therapy of breast cancer. *Front Biosci (Landmark Ed)*. 2011; 16:980–96. [PubMed: 21196213]
170. Yadav VR, Prasad S, Sung B, Kannappan R, Aggarwal BB. Targeting inflammatory pathways by triterpenoids for prevention and treatment of cancer. *Toxins (Basel)*. 2010; 2(10):2428–66. [PubMed: 22069560]
171. Dzubak P, Hajduch M, Vydra D, Hustova A, Kvasnica M, Biedermann D, Markova L, Urban M, Sarek J. Pharmacological activities of natural triterpenoids and their therapeutic implications. *Nat Prod Rep*. 2006; 23(3):394–411. [PubMed: 16741586]
172. Salminen A, Lehtonen M, Suuronen T, Kaarniranta K, Huuskonen J. Terpenoids: natural inhibitors of NF-kappaB signaling with anti-inflammatory and anticancer potential. *Cell Mol Life Sci*. 2008; 65(19):2979–99. [PubMed: 18516495]
173. Shanmugam MK, Dai X, Kumar AP, Tan BK, Sethi G, Bishayee A. Oleanolic acid and its synthetic derivatives for the prevention and therapy of cancer: preclinical and clinical evidence. *Cancer Lett*. 2014; 346(2):206–16. [PubMed: 24486850]
174. Pollier J, Goossens A. Oleanolic acid. *Phytochemistry*. 2012; 77:10–5. [PubMed: 22377690]
175. Ndlovu BC, Daniels WM, Mabandla MV. Oleanolic Acid enhances the beneficial effects of preconditioning on PC12 cells. *Parkinsons Dis*. 2014; 2014:929854. [PubMed: 25478286]
176. Zhao X, Liu M, Li D. Oleanolic acid suppresses the proliferation of lung carcinoma cells by miR-122/Cyclin G1/MEF2D axis. *Mol Cell Biochem*. 2015; 400(1–2):1–7. [PubMed: 25472877]
177. Nakao K, Miyaaki H, Ichikawa T. Antitumor function of microRNA-122 against hepatocellular carcinoma. *J Gastroenterol*. 2014; 49(4):589–93. [PubMed: 24531873]
178. Jung CJ, Iyengar S, Blahnik KR, Ajuha TP, Jiang JX, Farnham PJ, Zern M. Epigenetic modulation of miR-122 facilitates human embryonic stem cell self-renewal and hepatocellular carcinoma proliferation. *PLoS One*. 2011; 6(11):e27740. [PubMed: 22140464]
179. Castellano JM, Guinda A, Delgado T, Rada M, Cayuela JA. Biochemical basis of the antidiabetic activity of oleanolic acid and related pentacyclic triterpenes. *Diabetes*. 2013; 62(6):1791–9. [PubMed: 23704520]
180. Zhou X, Zeng XY, Wang H, Li S, Jo E, Xue CC, Tan M, Molero JC, Ye JM. Hepatic FoxO1 acetylation is involved in oleanolic acid-induced memory of glycemic control: novel findings from Study 2. *PLoS One*. 2014; 9(9):e107231. [PubMed: 25222566]
181. Ikeda Y, Murakami A, Ohigashi H. Ursolic acid: an anti- and pro-inflammatory triterpenoid. *Mol Nutr Food Res*. 2008; 52(1):26–42. [PubMed: 18203131]
182. Gupta MB, Bhalla TN, Gupta GP, Mitra CR, Bhargava KP. Anti-inflammatory activity of natural products. I. Triterpenoids. *Eur J Pharmacol*. 1969; 6(1):67–70. [PubMed: 5784648]
183. Liu J. Pharmacology of oleanolic acid and ursolic acid. *J Ethnopharmacol*. 1995; 49(2):57–68. [PubMed: 8847885]
184. Zang LL, Wu BN, Lin Y, Wang J, Fu L, Tang ZY. Research progress of ursolic acid's anti-tumor actions. *Chin J Integr Med*. 2014; 20(1):72–9. [PubMed: 24374755]
185. Chen IH, Lu MC, Du YC, Yen MH, Wu CC, Chen YH, Hung CS, Chen SL, Chang FR, Wu YC. Cytotoxic triterpenoids from the stems of *Microtropis japonica*. *J Nat Prod*. 2009; 72(7):1231–6. [PubMed: 19534471]
186. Wang J, Li Y, Wang X, Jiang C. Ursolic acid inhibits proliferation and induces apoptosis in human glioblastoma cell lines U251 by suppressing TGF-beta1/miR-21/PDCD4 pathway. *Basic Clin Pharmacol Toxicol*. 2012; 111(2):106–12. [PubMed: 22353043]
187. Singh PK, Campbell MJ. The Interactions of microRNA and Epigenetic Modifications in Prostate Cancer. *Cancers (Basel)*. 2013; 5(3):998–1019. [PubMed: 24202331]
188. Liby KT, Yore MM, Sporn MB. Triterpenoids and rexinoids as multifunctional agents for the prevention and treatment of cancer. *Nat Rev Cancer*. 2007; 7(5):357–69. [PubMed: 17446857]

189. Liby KT, Sporn MB. Synthetic oleanane triterpenoids: multifunctional drugs with a broad range of applications for prevention and treatment of chronic disease. *Pharmacol Rev.* 2012; 64(4):972–1003. [PubMed: 22966038]
190. Yore MM, Kettenbach AN, Sporn MB, Gerber SA, Liby KT. Proteomic analysis shows synthetic oleanane triterpenoid binds to mTOR. *PLoS One.* 2011; 6(7):e22862. [PubMed: 21818401]
191. Wang YY, Zhe H, Zhao R. Preclinical evidences toward the use of triterpenoid CDDO-Me for solid cancer prevention and treatment. *Mol Cancer.* 2014; 13:30. [PubMed: 24552536]
192. Tabe Y, Konopleva M, Kondo Y, Contractor R, Tsao T, Konoplev S, Shi Y, Ling X, Watt JC, Tsutsumi-Ishii Y, Ohsaka A, Nagaoka I, Issa JP, Kogan SC, Andreeff M. PPARgamma-active triterpenoid CDDO enhances ATRA-induced differentiation in APL. *Cancer Biol Ther.* 2007; 6(12):1967–77. [PubMed: 18075297]
193. Wang YY, Yang YX, Zhe H, He ZX, Zhou SF. Bardoxolone methyl (CDDO-Me) as a therapeutic agent: an update on its pharmacokinetic and pharmacodynamic properties. *Drug Des Devel Ther.* 2014; 8:2075–88.
194. Deeb D, Brigolin C, Gao X, Liu Y, Pindolia KR, Gautam SC. Induction of Apoptosis in Pancreatic Cancer Cells by CDDO-Me Involves Repression of Telomerase through Epigenetic Pathways. *J Carcinog Mutagen.* 2014; 5:177. [PubMed: 25152840]
195. Hartmann RM, Morgan Martins MI, Tieppo J, Fillmann HS, Marroni NP. Effect of *Boswellia serrata* on antioxidant status in an experimental model of colitis rats induced by acetic acid. *Dig Dis Sci.* 2012; 57(8):2038–44. [PubMed: 22451119]
196. Kruger P, Daneshfar R, Eckert GP, Klein J, Volmer DA, Bahr U, Muller WE, Karas M, Schubert-Zsilavecz M, Abdel-Tawab M. Metabolism of boswellic acids in vitro and in vivo. *Drug Metab Dispos.* 2008; 36(6):1135–42. [PubMed: 18356270]
197. Abdel-Tawab M, Werz O, Schubert-Zsilavecz M. *Boswellia serrata*: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet.* 2011; 50(6):349–69. [PubMed: 21553931]
198. Chaturvedi D, Dwivedi P, Chaturvedi A, Mishra N, Siddiqui HH, Mishra V. Semisynthetic hybrids of boswellic acids: a novel class of potential anti-inflammatory and anti-arthritis agents. *Medicinal Chemistry Research.* 2015:1–14.
199. Park B, Prasad S, Yadav V, Sung B, Aggarwal BB. Boswellic acid suppresses growth and metastasis of human pancreatic tumors in an orthotopic nude mouse model through modulation of multiple targets. *PLoS One.* 2011; 6(10):e26943. [PubMed: 22066019]
200. Yadav VR, Prasad S, Sung B, Gelovani JG, Guha S, Krishnan S, Aggarwal BB. Boswellic acid inhibits growth and metastasis of human colorectal cancer in orthotopic mouse model by downregulating inflammatory, proliferative, invasive and angiogenic biomarkers. *Int J Cancer.* 2012; 130(9):2176–84. [PubMed: 21702037]
201. Shen Y, Takahashi M, Byun HM, Link A, Sharma N, Balaguer F, Leung HC, Boland CR, Goel A. Boswellic acid induces epigenetic alterations by modulating DNA methylation in colorectal cancer cells. *Cancer Biol Ther.* 2012; 13(7):542–52. [PubMed: 22415137]
202. Takahashi M, Sung B, Shen Y, Hur K, Link A, Boland CR, Aggarwal BB, Goel A. Boswellic acid exerts antitumor effects in colorectal cancer cells by modulating expression of the let-7 and miR-200 microRNA family. *Carcinogenesis.* 2012; 33(12):2441–9. [PubMed: 22983985]
203. Rastogi V, Santiago-Moreno J, Dore S. Ginseng: a promising neuroprotective strategy in stroke. *Front Cell Neurosci.* 2014; 8:457. [PubMed: 25653588]
204. Choi JS, Chun KS, Kundu J, Kundu JK. Biochemical basis of cancer chemoprevention and/or chemotherapy with ginsenosides (Review). *Int J Mol Med.* 2013; 32(6):1227–38. [PubMed: 24126942]
205. Murthy HN, Georgiev MI, Kim YS, Jeong CS, Kim SJ, Park SY, Paek KY. Ginsenosides: prospective for sustainable biotechnological production. *Appl Microbiol Biotechnol.* 2014; 98(14):6243–54. [PubMed: 24859520]
206. Shi Q, Li J, Feng Z, Zhao L, Luo L, You Z, Li D, Xia J, Zuo G, Chen D. Effect of ginsenoside Rh2 on the migratory ability of HepG2 liver carcinoma cells: recruiting histone deacetylase and inhibiting activator protein 1 transcription factors. *Mol Med Rep.* 2014; 10(4):1779–85. [PubMed: 25051397]

207. An IS, An S, Kwon KJ, Kim YJ, Bae S. Ginsenoside Rh2 mediates changes in the microRNA expression profile of human non-small cell lung cancer A549 cells. *Oncol Rep.* 2013; 29(2):523–8. [PubMed: 23152132]
208. Wu N, Wu GC, Hu R, Li M, Feng H. Ginsenoside Rh2 inhibits glioma cell proliferation by targeting microRNA-128. *Acta Pharmacol Sin.* 2011; 32(3):345–53. [PubMed: 21372826]
209. Sato F, Tsuchiya S, Meltzer SJ, Shimizu K. MicroRNAs and epigenetics. *FEBS J.* 2011; 278(10):1598–609. [PubMed: 21395977]
210. Chan LS, Yue PY, Mak NK, Wong RN. Role of microRNA-214 in ginsenoside-Rg1-induced angiogenesis. *Eur J Pharm Sci.* 2009; 38(4):370–7. [PubMed: 19733659]
211. Suzuki H, Maruyama R, Yamamoto E, Kai M. Epigenetic alteration and microRNA dysregulation in cancer. *Front Genet.* 2013; 4:258. [PubMed: 24348513]
212. Lv X, Jiang H, Liu Y, Lei X, Jiao J. MicroRNA-15b promotes neurogenesis and inhibits neural progenitor proliferation by directly repressing TET3 during early neocortical development. *EMBO Rep.* 2014; 15(12):1305–14. [PubMed: 25344561]
213. Jin SG, Jiang Y, Qiu R, Rauch TA, Wang Y, Schackert G, Krex D, Lu Q, Pfeifer GP. 5-Hydroxymethylcytosine is strongly depleted in human cancers but its levels do not correlate with IDH1 mutations. *Cancer Res.* 2011; 71(24):7360–5. [PubMed: 22052461]
214. Liu C, Liu L, Chen X, Shen J, Shan J, Xu Y, Yang Z, Wu L, Xia F, Bie P, Cui Y, Bian XW, Qian C. Decrease of 5-hydroxymethylcytosine is associated with progression of hepatocellular carcinoma through downregulation of TET1. *PLoS One.* 2013; 8(5):e62828. [PubMed: 23671639]
215. Liu WR, Tian MX, Jin L, Yang LX, Ding ZB, Shen YH, Peng YF, Zhou J, Qiu SJ, Dai Z, Fan J, Shi YH. High expression of 5-hydroxymethylcytosine and isocitrate dehydrogenase 2 is associated with favorable prognosis after curative resection of hepatocellular carcinoma. *J Exp Clin Cancer Res.* 2014; 33:32. [PubMed: 24716838]
216. Orr BA, Haffner MC, Nelson WG, Yegnasubramanian S, Eberhart CG. Decreased 5-hydroxymethylcytosine is associated with neural progenitor phenotype in normal brain and shorter survival in malignant glioma. *PLoS One.* 2012; 7(7):e41036. [PubMed: 22829908]
217. Chan LS, Yue PY, Wong YY, Wong RN. MicroRNA-15b contributes to ginsenoside-Rg1-induced angiogenesis through increased expression of VEGFR-2. *Biochem Pharmacol.* 2013; 86(3):392–400. [PubMed: 23688497]
218. Kang KA, Piao MJ, Kim KC, Zheng J, Yao CW, Cha JW, Kim HS, Kim DH, Bae SC, Hyun JW. Compound K, a metabolite of ginseng saponin, inhibits colorectal cancer cell growth and induces apoptosis through inhibition of histone deacetylase activity. *Int J Oncol.* 2013; 43(6):1907–14. [PubMed: 24100442]
219. Park EH, Kim YJ, Yamabe N, Park SH, Kim HK, Jang HJ, Kim JH, Cheon GJ, Ham J, Kang KS. Stereospecific anticancer effects of ginsenoside Rg3 epimers isolated from heat-processed American ginseng on human gastric cancer cell. *J Ginseng Res.* 2014; 38(1):22–7. [PubMed: 24558306]
220. Shan X, Fu YS, Aziz F, Wang XQ, Yan Q, Liu JW. Ginsenoside Rg3 inhibits melanoma cell proliferation through down-regulation of histone deacetylase 3 (HDAC3) and increase of p53 acetylation. *PLoS One.* 2014; 9(12):e115401. [PubMed: 25521755]
221. Rogan EG. The natural chemopreventive compound indole-3-carbinol: state of the science. *In Vivo.* 2006; 20(2):221–8. [PubMed: 16634522]
222. Li Y, Li X, Guo B. Chemopreventive agent 3,3'-diindolylmethane selectively induces proteasomal degradation of class I histone deacetylases. *Cancer Res.* 2010; 70(2):646–54. [PubMed: 20068155]
223. Busbee PB, Nagarkatti M, Nagarkatti PS. Natural indoles, indole-3-carbinol and 3,3'-diindolylmethane, inhibit T cell activation by staphylococcal enterotoxin B through epigenetic regulation involving HDAC expression. *Toxicol Appl Pharmacol.* 2014; 274(1):7–16. [PubMed: 24200994]
224. Beaver LM, Yu TW, Sokolowski EI, Williams DE, Dashwood RH, Ho E. 3,3'-Diindolylmethane, but not indole-3-carbinol, inhibits histone deacetylase activity in prostate cancer cells. *Toxicol Appl Pharmacol.* 2012; 263(3):345–51. [PubMed: 22800507]

225. Wong CP, Hsu A, Buchanan A, Palomera-Sanchez Z, Beaver LM, Houseman EA, Williams DE, Dashwood RH, Ho E. Effects of sulforaphane and 3,3'-diindolylmethane on genome-wide promoter methylation in normal prostate epithelial cells and prostate cancer cells. *PLoS One*. 2014; 9(1):e86787. [PubMed: 24466240]
226. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. *J Clin Gastroenterol*. 2006; 40(3):235–43. [PubMed: 16633129]
227. Rynningen A, Stapnes C, Lassalle P, Corbascio M, Gjertsen BT, Bruserud O. A subset of patients with high-risk acute myelogenous leukemia shows improved peripheral blood cell counts when treated with the combination of valproic acid, theophylline and all-trans retinoic acid. *Leuk Res*. 2009; 33(6):779–87. [PubMed: 19007987]
228. Fredly H, Gjertsen BT, Bruserud O. Histone deacetylase inhibition in the treatment of acute myeloid leukemia: the effects of valproic acid on leukemic cells, and the clinical and experimental evidence for combining valproic acid with other antileukemic agents. *Clin Epigenetics*. 2013; 5(1):12. [PubMed: 23898968]
229. Coronel J, Cetina L, Pacheco I, Trejo-Becerril C, Gonzalez-Fierro A, de la Cruz-Hernandez E, Perez-Cardenas E, Taja-Chayeb L, Arias-Bofill D, Candelaria M, Vidal S, Duenas-Gonzalez A. A double-blind, placebo-controlled, randomized phase III trial of chemotherapy plus epigenetic therapy with hydralazine valproate for advanced cervical cancer. Preliminary results. *Med Oncol*. 2011; 28(Suppl 1):S540–6. [PubMed: 20931299]
230. Kang SH, Seok YM, Song MJ, Lee HA, Kurz T, Kim I. Histone Deacetylase Inhibition Attenuates Cardiac Hypertrophy and Fibrosis through Acetylation of Mineralocortic Receptor in Spontaneously Hypertensive Rats. *Mol Pharmacol*. 2015
231. Isoherranen N, Yagen B, Bialer M. New CNS-active drugs which are second-generation valproic acid: can they lead to the development of a magic bullet? *Curr Opin Neurol*. 2003; 16(2):203–11. [PubMed: 12644750]
232. Trojnar MK, Wierzchowska-Cioch E, Krzyzanowski M, Jargiello M, Czuczwar SJ. New generation of valproic acid. *Pol J Pharmacol*. 2004; 56(3):283–8. [PubMed: 15215557]
233. Hemshekhar M, Sebastin Santhosh M, Kemparaju K, Girish KS. Emerging roles of anacardic acid and its derivatives: a pharmacological overview. *Basic Clin Pharmacol Toxicol*. 2012; 110(2):122–32. [PubMed: 22103711]
234. Eliseeva ED, Valkov V, Jung M, Jung MO. Characterization of novel inhibitors of histone acetyltransferases. *Mol Cancer Ther*. 2007; 6(9):2391–8. [PubMed: 17876038]
235. Balasubramanyam K, Altaf M, Varier RA, Swaminathan V, Ravindran A, Sadhale PP, Kundu TK. Polyisoprenylated benzophenone, garcinol, a natural histone acetyltransferase inhibitor, represses chromatin transcription and alters global gene expression. *J Biol Chem*. 2004; 279(32):33716–26. [PubMed: 15155757]
236. Mantelingu K, Reddy BA, Swaminathan V, Kishore AH, Siddappa NB, Kumar GV, Nagashankar G, Natesh N, Roy S, Sadhale PP, Ranga U, Narayana C, Kundu TK. Specific inhibition of p300-HAT alters global gene expression and represses HIV replication. *Chem Biol*. 2007; 14(6):645–57. [PubMed: 17584612]
237. Sethi R, Sethi R, Redmond A, Lavik E. Olfactory ensheathing cells promote differentiation of neural stem cells and robust neurite extension. *Stem Cell Rev*. 2014; 10(6):772–85. [PubMed: 24996386]
238. Delage B, Dashwood RH. Dietary manipulation of histone structure and function. *Annu Rev Nutr*. 2008; 28:347–66. [PubMed: 18598138]
239. Stronach EA, Alfraidi A, Rama N, Datler C, Studd JB, Agarwal R, Guney TG, Gourley C, Hennessy BT, Mills GB, Mai A, Brown R, Dina R, Gabra H. HDAC4-regulated STAT1 activation mediates platinum resistance in ovarian cancer. *Cancer Res*. 2011; 71(13):4412–22. [PubMed: 21571862]
240. Milenkovic D, Deval C, Gouranton E, Landrier JF, Scalbert A, Morand C, Mazur A. Modulation of miRNA expression by dietary polyphenols in apoE deficient mice: a new mechanism of the action of polyphenols. *PLoS One*. 2012; 7(1):e29837. [PubMed: 22253797]

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	<i>type 2 Diabetes</i>	[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]