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Histone and Non-Histone Targets of Dietary Deacetylase Inhibitors

Eunah Kim¹, William H. Bisson³, Christiane V. Löhr², David E. Williams^{3,5}, Emily Ho^{4,5}, Roderick H. Dashwood^{1,6,7,8}, and Praveen Rajendran^{1,*}

¹Center for Epigenetics & Disease Prevention, Institute of Biosciences & Technology, Texas A&M Health Science Center, Houston, TX, USA

²College of Veterinary Medicine, Oregon State University, Corvallis, OR, USA

³Department of Environmental and Molecular Toxicology, Oregon State University, Corvallis, OR, USA

⁴Biological and Population Health Sciences, Oregon State University, Corvallis, OR, USA

⁵Linus Pauling Institute, Oregon State University, Corvallis, OR, USA

⁶Department of Nutrition & Food Science, Texas A&M University, College Station, TX, USA

⁷Department of Clinical Cancer Prevention, MD Anderson Cancer Center, Houston, TX, USA

⁸Department of Molecular & Cellular Medicine, Texas A&M University College of Medicine, College Station, TX, USA

Abstract

Acetylation is an important, reversible post-translational modification affecting histone and non-histone proteins with critical roles in gene transcription, DNA replication, DNA repair, and cell cycle progression. Key regulatory enzymes include histone deacetylase (HDACs) and histone acetyltransferases (HATs). Overexpressed HDACs have been identified in many human cancers, resulting in repressed chromatin states that interfere with vital tumor suppressor functions.

Inhibition of HDAC activity has been pursued as a mechanism for re-activating repressed genes in cancers, with some HDAC inhibitors showing promise in the clinical setting. Dietary compounds and their metabolites also have been shown to modulate HDAC activity or expression. Out of this body of research, attention increasingly has shifted towards non-histone targets of HDACs and HATs, such as transcription factors, hormone receptors, DNA repair proteins, and cytoskeletal components. These aspects are covered in present review, along with the possible clinical significance. Where such data are available, examples are cited from the literature of studies with short chain fatty acids, polyphenols, isoflavones, indoles, organosulfur compounds, organoselenium compounds, sesquiterpene lactones, isoflavones, and various miscellaneous agents. By virtue of their effects on both histone and non-histone proteins, dietary

*Correspondence should be addressed to P. R. (prajendran@ibt.tamhsc.edu); Dr. Praveen Rajendran, Center for Epigenetics & Disease Prevention, 2121 West Holcombe Blvd., Houston, TX 77030; Phone: +1-713-677-7803.

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chemopreventive agents modulate the cellular acetylome in ways that are only now becoming apparent. A better understanding of the molecular mechanisms will likely enhance the potential to more effectively combat diseases harboring altered epigenetic landscapes and dysregulated protein signaling.

Dietary chemopreventive agents modulate the cellular acetylome by affecting both histone and non-histone proteins, which will likely enhance their potential to more effectively combat diseases harboring altered epigenetic landscapes.

Graphical abstract

Keywords

Acetylation; diet; epigenetics; phytochemicals; HDAC; non-histone

1. INTRODUCTION

1.1 HDAC inhibition and histone acetylation

The genome is organized into arrays of nucleosomes composed of histones and DNA. The nucleosome is a fundamental and highly dynamic unit consisting of chromatin structures involved in key cellular functions such as cell cycle progression, mitosis, DNA replication, DNA damage recognition, DNA repair, heterochromatin silencing, and gene transcription. During such processes, histones are post-translationally modified in various ways, including methylation, ubiquitination, phosphorylation, and acetylation¹. Acetylation on histones neutralizes their positive charge, decreasing the interactions with negatively charged DNA and associated regulatory proteins. This open or “euchromatin” conformation allows genes

to be actively transcribed². In contrast, deacetylation of histones results in condensation, or “heterochromatin”, leading to gene repression.

Histone acetylation is regulated in large measure by the opposing actions of histone acetyltransferases (HATs), which add acetyl groups, and histone deacetylases (HDACs), which remove the acetyl groups³. Acetylation and other post-translation modifications on N-terminal tails of histones influence the state of gene expression by providing a binding platform for various proteins, such as transcriptional factors, chromatin remodeling/modifying components, and co-activators/repressors⁴. Thus, manipulation of histone acetylation through HDAC inhibition has been proposed as a mechanism for derepressing genes dysregulated in chronic conditions such as cancer, neurodegenerative diseases, psychological disorders, and lung pathologies.

At present, 18 HDACs have been identified in humans that fall into four classes: class I HDACs (HDAC1, HDAC2, HDAC3 and HDAC8) are localized mainly in the nucleus, class II HDACs (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9 and HDAC10) are restricted to certain tissues and can be present in both nuclear and cytoplasmic compartments, class III HDACs are NAD-dependent sirtuins (SIRT1 to SIRT7), and HDAC11, the only class IV HDAC, which shares conserved residues with both class I and II HDACs⁵. Non-sirtuin HDACs are zinc-dependent enzymes.

The online website clinicaltrials.gov lists numerous human trials with HDAC inhibitors, either as monotherapies or combination treatments. Vorinostat and Romidepsin are the best-studied HDAC inhibitors, approved by the US Food and Drug Administration (FDA) for the treatment of advanced cutaneous T-cell lymphoma. However, the list of HDAC inhibitors is growing rapidly, and comprises compounds from unrelated chemical classes. Despite the different HDAC isoform specificity, these agents typically exhibit similar toxicity and resistance profiles⁶. This could be related to the fact that they share a common mechanistic theme, that is, inhibition of zinc-dependent functions, thus affecting all but the NAD-dependent sirtuins as “pan-HDAC inhibitors”.

For these reasons, the pursuit of novel and improved HDAC inhibitors has shifted towards dietary factors, isolated phytochemicals, and novel metabolites with wider safety margins or improved HDAC selectivity^{7, 8}. Mechanisms being pursued include direct binding to the catalytic site, as competitive HDAC inhibitors, or interactions with allosteric sites critical for protein-protein interactions (e.g., in HDAC/co-repressor complexes). Other dietary compounds affect HDAC expression and stability indirectly, for example, via kinase-mediated mechanisms and ubiquitylation pathways (Fig. 1). Such mechanisms often involve cross-talk among post-translational modifications, including acetylation changes on non-histone proteins.

1.2 Acetylation of non-histone proteins

Many non-histone proteins (transcription factors, regulators of DNA repair, recombination and replication, chaperones, viral proteins, and others) are subject to acetylation. Indeed, a recent investigation used high-resolution mass spectrometry to identify 3,600 separate acetylation sites in 1,750 human proteins, implicating lysine acetylation in the regulation of

nearly all nuclear functions and many cytoplasmic processes^{9, 10}. It is noteworthy that the non-histone targets are involved in cellular processes such as chromatin remodeling, cell cycle regulation, apoptosis, autophagy, and actin nucleation, which are dysregulated in cancer etiology¹⁰.

We have summarized some of the well-known non-histone protein targets for which the acetylation status is regulated by opposing actions of HATs and HDACs (Table 1). Unlike acetylation on histones, the acetylation of non-histone targets is associated with either activation or inactivation of protein function¹¹. These non-histone proteins regulate many key biological processes, including cell proliferation, cell survival, and apoptosis, with the acetylation status influencing protein stability, enzymatic activity, sub-cellular localization, protein–DNA interactions, and protein–protein partnering¹¹ (Fig 2).

The well-studied tumor suppressor p53 is subject to acetylation by p300/CBP at the C-terminal DNA binding domain¹². As a result, the activity of p53 is altered during the DNA damage response¹². Acetylation of p53 by p300/CBP is opposed by HDAC1, and subsequent steps can involve MDM2-mediated ubiquitination, leading to p53 turnover^{13, 14}. Thus, HATs and HDACs balance the acetylation status of p53 and fine-tune its stability and half-life. In contrast to the actions of HDAC1, deacetylation by the class III HDAC SIRT1 decreases the transcriptional activity of p53, and activates p21 in cell cycle regulation and DNA repair process¹⁵.

Another well-known transcription factor regulated by SIRT1 is signal transducer and activator of transcription 3 (STAT3), which has key roles in cytokine signaling¹⁶. Like phosphorylation, acetylation status influences dimerization, nuclear-cytoplasmic localization, and the transcriptional activity of STAT family members¹⁷. On histone tails, a phospho-acetyl switch has been identified^{18, 19}, for which parallels might exist in regulating STAT3 and other non-histone proteins.

Nuclear receptors also represent important non-histone targets for acetylation and deacetylation. Acetylation of the androgen receptor (AR) by p300/CBP and TIP60 at multiple lysines in the DNA binding domain enhances hormone-dependent transactivation, whereas deacetylation of AR by HDAC1 represses its function²⁰. Further, ubiquitination by MDM2 occurs upon removal of acetylation on AR¹⁴. Interestingly, in chronic obstructive pulmonary disease (COPD) and other lung pathologies, it is loss of HDAC2, not HDAC1, that is implicated in excessive GR signaling pathways^{7, 21, 22}.

In addition to transcription factors and nuclear receptors, the cytoskeletal protein α -tubulin is a well-recognized non-histone target for acetylation. Deacetylation of α -tubulin by HDAC6 and SIRT2 induces cell motility and enhances microtubule depolymerization^{23–25}. HDAC8 also associates with β -actin and, via changes in its acetylation status, regulates smooth muscle contractility²⁶.

In the following paragraphs, we further discuss protein acetylation in the context of dietary agents and their modulatory effects (Table 2), highlighting key mechanistic questions or gaps in the literature.

2.0 PROTEIN ACETYLATION AND DIETARY CHEMOPREVENTIVE AGENTS

2.1 Short Chain Fatty Acids

Short chain fatty acids (SCFAs) are the end product of fermentation of dietary fiber and they exhibit anticancer effects such as inhibition of proliferation, apoptosis induction, or cell cycle arrest^{27–29}. Such effects are thought to be mediated *via* the inhibition of HDAC activity. In many studies, SCFA treatment resulted in hyper acetylation of histone H3 and/or H4 and the activation of tumor suppressor and oxidative stress response genes in cancer cells^{27, 30}. Sodium butyrate (IC₅₀: 0.3 mM) was reported over three decades ago to induce histone acetylation in cultured leukemia cells^{31, 32}. However, it was not formally identified as an HDAC inhibitor until quite recently. *In vitro*, butyrate acts as a competitive HDAC inhibitor, with an apparent K_i of 46 μM when tested in whole cell lysates of human MCF-7 breast cancer cells, compared with an apparent K_i of 1 nM for trichostatin A (TSA) under the same conditions³³. Interestingly, butyrate and pyruvate have been reported as selective inhibitors of HDAC1 and HDAC3, whereas lactate, a precursor in the pathway of carbohydrate metabolism, had no such effect on HDAC activity^{34, 35}. These results are surprising since butyrate is usually thought of as a class I HDAC inhibitor (if not a pan HDAC inhibitor) that has both histone and non-histone targets, for example HMG protein in colon cancer cells^{36, 37, 38}. Tributyrin and valproic acid (IC₅₀: 39 μM~2mM) are other small molecule HDAC inhibitors in the same category^{39, 40, 41}. Tributyrin shares *p21 WAF1* as a common gene target for de-repression in cancer cells⁴¹. Similar to butyrate, tributyrin has also been shown to acetylate p53⁴², and valproic acid has been shown to acetylate Ku70 in medulloblastoma cells⁴³. More recently, it was reported that the ketone body d-β-hydroxybutyrate (βOHB) (IC₅₀: 2~5mM) is an endogenous and specific inhibitor of class I HDACs. Treatment of cells with βOHB increased global histone acetylation and activated oxidative stress genes such as *FOXO3A* and *MT2* through inhibition of HDAC1 and HDAC2⁴⁴.

2.2 Selenium

Selenium is an essential trace element found in the soil, and is also bio-accumulated as organic forms in foods such as Brazil nuts, cruciferous vegetables, and allium vegetables. Anticancer effects of selenium compounds have been reported in various cancer cell lines such as colon, prostate, and ovary⁴⁵. In addition, metabolites of organoselenium compounds have been implicated in regulating gene expression via epigenetic mechanisms. For example, methylseleninic acid (MSA) inhibited the growth of esophageal squamous cell carcinoma cells¹¹⁸ and diffuse large B-cell lymphoma cell lines¹¹⁹, and this was associated with decreased HDAC activity. In the former study, MSA acetylated both histone and non-histone proteins, such as α-tubulin, and this required conversion to its presumed metabolites methylselenol and dimethylselenide¹¹⁸. Recently, we reported that a novel seleno-α-keto acid, methylselenopyruvate (MSP) (IC₅₀: 20 μM), triggered global histone acetylation in human colon cancer cells and in several other cancer cell lines. Apoptosis was activated via direct transcriptional changes on the gene promoter for *Bcl-2-modifying factor* (*BMF*)²⁶. Based on our data, HDAC8 de-recruitment rather than STAT3 acetylation likely served as the primary driver of *BMF* transcriptional activity in response to MSP²⁶.

2.3 Isothiocyanates

Brassica or cruciferous vegetables are a rich source of glucosinolates. The hydrolysis of these glucosinolates by the plant enzyme myrosinase generates biologically active isothiocyanates (ITC)¹⁶⁷ and indoles¹⁶⁸. Many studies have shown that ITCs exert anti-cancer effects through inhibition of HDAC activity and histone hyperacetylation, as reported for sulforaphane (SFN)^{169, 170}, allyl isothiocyanate (allyl-ITC)⁹⁵, benzyl isothiocyanate (BITC)⁹⁶, phenylhexyl isothiocyanate (PHITC)⁹⁸, phenethyl isothiocyanate (PEITC)¹⁰², and other longer-chain isothiocyanates¹⁷¹.

BITC decreased HDAC activity and the expression levels of HDAC1 and HDAC3 proteins in Capan-2 and BxPC-3 pancreatic cancer cells, but not in normal cells⁹⁶. HDAC inhibition by BITC resulted in histone hyperacetylation on the *p21WAF1* gene, induction of p21^{waf1} protein expression, and cell cycle arrest. Recently, Xiao *et al.* reported that BITC induced autophagy by increasing acetylation of FoxO1, a non-histone target, in breast cancer cells⁹⁷.

In silico studies have indicated that metabolites of dietary ITCs have structural features similar to pharmacological HDAC inhibitors, allowing them to dock into the HDAC catalytic site^{169, 171} or bind to allosteric sites on HDAC complexes⁹⁴. In addition to histone targets, ITCs have been reported to alter the acetylation status of non-histone proteins. SFN decreased HDAC3 and/or HDAC6 protein expression in colon and prostate cancer cells, leading to hyperacetylation of histones and α -tubulin^{172, 93, 173}. Others have examined such relationships in keratinocytes⁸⁹ and lymphocytes¹⁷⁴. In the latter study, SFN increased histone acetylation and attenuated lymphocyte HDAC activity to control levels¹⁷⁴.

We reported that SFN and related longer-chain ITCs induced DNA damage in colon cancer cells, but not in normal colonic epithelial cells⁹⁴. DNA damage was associated with acetylation and turnover of C-terminal binding protein interacting protein (CtIP), a key component of DNA repair pathways involving homologous recombination and DNA repair⁹⁴. Data from *in vivo* studies revealed that targeted magnetic microspheres containing SFN inhibited tumor growth and reduced histone deacetylase levels in C57BL/6 mice¹⁷⁵. In the prostate cancer (TRAMP) model, SFN also attenuated the expression levels of HDAC1, HDAC4, and HDAC7⁹¹.

PEITC is another promising chemopreventive agent, with efficacy in preclinical models against various types of cancer¹⁷⁶. PEITC has been found to affect both promoter demethylation and the chromatin states in prostate cancer cells, re-activating genes such as *glutathione S-transferase P1* (GSTP1)^{177, 178}. Recently, Chang *et al.* reported that PEITC mediated α -tubulin acetylation in breast cancer cells, although they did not formally test the hypothesis that PEITC might selectively target HDAC6 or its α -tubulin deacetylase activity¹⁰³.

2.4 Indole-3-carbinol and 3,3'-diindolylmethane

Cruciferous vegetables contain glucosinolates such as glucobrassicin, the precursor of indole-3-carbinol (I3C) (IC₅₀: 0.1–20 μ M). I3C and its acid condensation products, such as 3,3'-diindolylmethane (DIM) (IC₅₀: 0.1–20 μ M), have been examined extensively for their cancer chemoprotective properties¹⁷⁹. Bhatnagar *et al.* reported that DIM inhibited the

expression of HDAC1, HDAC2 and HDAC3 in colon cancer cells leading to inhibition of Survivin mRNA and protein expression¹⁰⁶. Li *et al.* demonstrated that DIM-induced HDAC depletion involved proteasome-mediated HDAC protein turnover¹⁰⁴. Although the authors found negligible increases in the acetylation of histones associated with selected gene promoters, a reduction in the levels of repressive HDACs bound to the *p21WAF1* and *p27* promoters coincided with cell cycle arrest¹⁰⁴. Beaver *et al.* recently reported that DIM significantly inhibited HDAC activity and reduced HDAC2 expression in both androgen sensitive and insensitive prostate cancer cells, and this was correlated with increased expression of *p21WAF1*¹⁰⁵. In mice, Staphylococcal enterotoxin B (SEB)-induced activation of T cells was attenuated by I3C and DIM treatment, and this was associated with the inhibition of class I HDACs¹⁰⁷.

2.5 Parthenolide

Parthenolide (PN) is a sesquiterpene lactone of the germacranolide class isolated from *Tanacetum parthenium* and found in many flowers and fruits. In addition to its other actions, PN treatment was associated with depleting HDAC1 protein without affecting other class I/II HDACs¹⁰⁸. Recently, PN was shown to inhibit tumorigenesis due to the activation of *p21WAF1* and repression of *CYCLIN D1*, with evidence for alteration in local histone H3 acetylation^{180, 108}, but perhaps involving non-histone targets of HDAC1.

2.6 Allium compounds

Garlic, onions, shallots and other members of the allium family contain an interesting mix of water-soluble and fat-soluble organosulfur compounds, some of which have been implicated as chemopreventive agents^{45, 181}. Allyl derivatives from garlic were among the first compounds described to impact histone acetylation status in cancer cells. Allyl mercaptan (AM), diallyl disulfide (DADS), S-allylcysteine (SAC), S-allylmercaptocysteine (SAMC) and allicin increased histone acetylation in various human cancer cells^{95, 115–117}, implicating HDACs as possible targets. AM was the most effective HDAC inhibitor among several garlic-derived organosulfur compounds tested *in vitro*¹¹⁴. Based on the IC₅₀ values, intracellular metabolism to small molecular thiols, such as AM, likely accounts for most of the HDAC inhibition associated with garlic organosulfur compounds. At relatively low concentrations, AM caused histone H3 hyperacetylation in human colon cancer cells, and facilitated Sp3 and p53 binding on the *p21WAF1* promoter¹¹⁴.

Several reports suggest that DADS can induce histone acetylation, as shown in leukemia¹¹¹, colon¹¹³, breast¹¹² and prostate¹⁸² cancer cells. DADS treatment also triggered global histone hyperacetylation during adipocyte differentiation¹¹⁰. Further, adipocyte differentiation-related genes such as *LPL*, *FAS*, *SREBP1c*, *aP2* and *PPAR-γ* were increased, while *PREF-1*, a preadipocyte marker gene, was decreased by DADS. These findings suggested that DADS affects adipocyte differentiation through histone acetylation at an early phase¹¹⁰. *In vivo* studies with DADS revealed increased histone acetylation in rat colonocytes¹⁸³. Although metabolites of DADS are thought to act as HDAC inhibitors in various cancer cell lines, one group focused on DADS and its ability to decrease the activity and expression of N-acetyltransferase (NAT) in human esophagus epidermoid carcinoma CE 81T/VGH cells¹⁰⁹.

Whereas global and local histone acetylation is induced under such conditions, little is known about the specific HDACs affected. Molecular docking and enzyme kinetics studies supported AM-HDAC8 interactions¹¹⁴, but other HDACs remain to be examined. If, indeed, the final common metabolite generated by such organosulfur compounds is AM, the small size and highly reactive sulfhydryl group would predict ready access and strong interactions with the active site zinc atom in multiple HDACs. This lack of HDAC specificity might offer no greater benefit over currently used pan-HDAC inhibitors undergoing clinical trials.

2.7 Polyphenols

2.7.1 Epigallocatechin-3-gallate—Polyphenols occur naturally in many foods and beverages, including green tea, curry spices, grapes, soy, and berries. (–)-Epigallocatechin-3-gallate (EGCG) is the most abundant polyphenol in green tea. Although it was first identified as an “antioxidant” *in vitro*¹⁸⁴, the possible relevance of this “antioxidant” activity to anticancer properties of EGCG is far from established *in vivo*. EGCG was reported to inhibit enzymes involved in DNA methylation, and was subsequently identified as a histone modifier^{122, 125, 126}. EGCG inhibited HDAC activity and increased histone acetylation in prostate¹²², skin¹²⁵, and breast cancer cells¹²⁶. Pandey *et al.* demonstrated that EGCG reduced mRNA expression of *HDAC1*, *HDAC2*, and *HDAC3*, leading to re-expression of *GSTP1* in prostate cancer cells¹²². In human oral squamous carcinoma cells, EGCG decreased SIRT3 activity and expression¹⁸⁵.

Li *et al.* showed that EGCG reactivated the estrogen receptor (*ERα*) in breast cancer cells, due to decreased binding of a transcription repressor complex containing HDAC1 (Rb/p130-E2F4/5-HDAC1-SUV39H1-DNMT1)¹²⁶. On the contrary, Choi *et al.* identified EGCG as a HAT inhibitor that suppressed transcription factor p65 (RelA) acetylation, thereby inhibiting nuclear factor kappa B (*NFκB*), interleukin 6 (*IL6*), and other downstream target genes¹²⁴.

In addition to the HAT and HDAC modulatory activities, EGCG also inhibited polycomb group (PcG) proteins, such as Ezh2¹²³. Reduced Ezh2 and HDAC1 levels at the *TIMP-3* gene were associated with a decrease in the histone repressive mark H3K27me3, and an increase in the activation mark H3K9/18ac¹²³. EGCG also was shown to prevent hydrogen peroxide-induced senescence in human dermal fibroblasts by the suppression of p53 acetylation, indicating that p53 is a non-histone target of EGCG¹²⁷. In human prostate cancer cells, EGCG inhibited class I HDACs to activate p53 transcriptional activity, via increased acetylation on p53¹²⁸. Recently, Liu *et al.* reported that EGCG is involved in acetylating FoxO1 in high-glucose treated H9c2 cardiomyoblasts¹²⁹. Acetylated FoxO1 was associated with increased reactive oxygen species (ROS) and autophagy pathways in cardiomyoblasts. Another non-histone target for EGCG is the androgen receptor (AR), which is regulated by acetylation in prostate cancer cells¹³⁰. EGCG also has been reported to act via HAT inhibition¹³¹. In human lung cancer cells, EGCG treatment resulted in the deacetylation of Smad2 and Smad3, which inhibited TGF-β1-mediated epithelial-mesenchymal transition¹³¹.

2.7.2 Curcumin—Curcumin, a component of turmeric (*Curcuma longa*), has reported antioxidant, anti-inflammatory, and chemopreventive properties, although the underlying

molecular mechanisms have yet to be fully elucidated. In clinical studies, curcumin has been tested for its chemosensitizing potential. Like EGCG, curcumin has been evaluated as a p300 (HAT) inhibitor. Kang *et al.* observed that curcumin treatment resulted in histone hypoacetylation in brain cancer cells, and induced differentiation and cell death in neurons, but not astrocytes¹⁸⁶. This finding suggested that curcumin exerts selective HAT inhibitory activity in neural cancer stem cells. In another study, curcumin reduced DNA repair activity by inhibiting HATs and ATR¹⁸⁷. The authors showed that curcumin specifically suppressed homologous recombination by reducing the expression of the *BRCA1* gene, *via* altered histone acetylation at the *BRCA1* promoter¹⁸⁷. However, in other studies, curcumin was reported as an HDAC inhibitor, and increased histone acetylation¹³⁷ on gene promoters such as *suppressor of cytokine signaling* (SOCS) genes *SOCS1* and *SOCS3*¹³⁵ and *BAX*, a proapoptotic gene¹³⁶. Curcumin inhibited HDAC4 in medulloblastoma cells¹³³ and HDAC6 in leukemia (K-562 and HL-60) cell lines¹³⁴.

Curcumin also has been shown to affect non-histone protein acetylation. In cervical cancer cells, curcumin inhibited HDAC1 and HDAC2 activity and increased acetylation of p53¹³². Similar results were found in prostate cancer cells¹³⁸, and p53 acetylation was found to regulate its stability, transcriptional activity, and subcellular localization¹³⁸.

2.7.3 Resveratrol—Resveratrol is a polyphenolic phytoestrogen found in certain types of grapes and red wine. It has attracted attention due to reports on increased longevity, and the treatment of age-related diseases such as diabetes, neurodegeneration, and cancer. Different modes of action have been proposed for resveratrol, including the activation of sirtuins¹⁸⁸. Resveratrol has also been shown to inhibit sirtuins, e.g. SIRT2 in glioblastoma stem cells¹⁴⁰. Some reports have shown that resveratrol can also inhibit other HDACs. Indeed, Venturelli *et al.* demonstrated that resveratrol inhibited all classes of HDACs in a dose-dependent manner¹³⁹. Using *in silico* molecular docking, they showed that resveratrol fits into the active site of HDAC2, HDAC4, HDAC7, and HDAC8, and inhibits their deacetylase activity¹³⁹. Others reported that resveratrol increases histone and non-histone protein acetylation status, for example, associated with p53¹⁴¹, the nuclear bile acid receptor FXR⁸⁸, and PGC1 α ¹⁴², despite the fact that SIRT1 deacetylase activity may be enhanced under the same conditions. In another study, resveratrol increased acetylation on p53 and FOXO3a proteins in Hodgkin lymphoma-derived L-428 cells¹⁴³. Similar to resveratrol, piceatannol, another polyphenol found in red wine, is known to be a SIRT1 activator^{189–192}. Taken together, the results suggest that resveratrol may have differential effects on histone and non-histone protein acetylation, depending on the interplay between different HDACs.

2.7.4 Chrysin—Chrysin is a naturally-occurring flavone belonging to a group of polyphenolic compounds found in mushrooms, olive oil, tea, red wine, and passion fruit flowers, with antitumor effects in various cancer cells¹⁹³. Pal-Bhadra *et al.* showed that chrysin inhibited HDAC2 and HDAC8 activity in melanoma (A375) cells leading to histone acetylation and *p21WAF1* activation, via the recruitment of STAT1, STAT3, and STAT5 proteins to the corresponding gene promoter¹⁴⁴. Further studies are warranted on the apparent selective inhibition by chrysin of HDAC2 and HDAC8.

2.7.5 Ellagic acid—Ellagic acid is a naturally-occurring polyphenolic acid abundant in fruits and nuts, such as pomegranate, berries, and walnuts. Chemopreventive effects of ellagic acid have been observed against various cancers, including oral cancer, where it was recently shown to block the VEGF signaling pathway in a hamster model of oral cancer¹⁴⁵. The anti-angiogenic activity of ellagic acid can be mediated, in part, by blocking hypoxia and VEGF/VEGFR2 signaling pathways, through the suppression of HDAC6 and HIF-1 α ¹⁴⁵.

2.8 Isoflavones

2.8.1 Quercetin—Quercetin is a flavonoid naturally occurring in fruits, vegetables, leaves, and grains. Based on pharmacophore modeling, quercetin was predicted to bind to the SIRT6 catalytic pocket¹⁴⁷. Kokkonen *et al.* demonstrated that quercetin is a potent inhibitor of SIRT6, inducing histone acetylation (H3K56ac) in cultured cells¹⁴⁸. Interestingly, quercetin recruited p300 HAT to the promoter region of the *cyclooxygenase-2* (*COX-2*) gene, an important regulator of inflammation and tumorigenesis, thereby enhancing *COX-2* expression in melanoma cells¹⁹⁴.

2.8.2 Apigenin—Apigenin (4',5,7,-trihydroxyflavone) is a plant flavone abundant in grapefruit, parsley, and chamomile. Anticancer effects of apigenin involve mechanisms associated with cell cycle arrest and apoptosis¹⁹⁵. Activation of p53 and the generation of ROS were observed in prostate cancer cells treated with apigenin¹⁹⁶. Interestingly, Pandey *et al.* recently reported that apigenin inhibited the activity and expression of HDAC1 and HDAC3, leading to the acetylation of histones on the *p21 WAF1* gene, and apoptosis induction in human prostate cancer cells¹⁴⁹. Apigenin also is known to suppress DNA methylation levels by decreasing mRNA and protein levels of DNMT proteins in skin cancer cells¹⁹⁷.

2.8.3 Genistein—Genistein is abundantly found in soybeans and soy products and has been shown to prevent and inhibit breast cancer by activating tumor suppressors genes such as p21, p16 and ER α ¹⁹⁸. Genistein has been reported to have HDAC inhibitory properties in cancer cells¹⁵¹. It has been shown to inhibit HDAC1 in colon cancer cells¹⁵¹, HDAC6 and SIRT1 in prostate cancer cells^{199,152}, and cause histone methylation and acetylation changes in breast cancer cell lines²⁰⁰.

2.8.4 Luteolin—Luteolin is a flavone abundant in plants including fruits, vegetables, and medicinal herbs. Recently, Attoub *et al.* have shown that the anti-cancer and anti-metastatic properties of luteolin are associated with changes in histone acetylation¹⁵⁶. A computational modeling study has shown that luteolin can bind to SIRT6 protein¹⁴⁷.

2.9 Other dietary HDAC inhibitors

Queen bee phenotypes such as fertility and larvae size are determined at an early stage by differential nutrition with Royal jelly secreted from the nurse bees²⁰¹. Recently, Spannhoff *et al.* demonstrated that Royal jelly has HDAC inhibitory activity associated with (E)-10-hydroxy-2-decenoic acid (10HDA), a major component of Royal jelly¹⁵⁸. Structural

similarities between 10HDA and Vorinostat might explain the increased global histone acetylation levels and re-activation of the *FAS* gene in NIH3T3 cells¹⁵⁸.

Nicotinamide occurs in meat, fish, nuts, and mushrooms, as well as to a lesser extent in some vegetables. Nicotinamide is believed to be a pan-sirtuin inhibitor, and has demonstrated sirtuin inhibitory activity in gastric cancer²⁰², lung cancer²⁰³, and breast cancer cells²⁰⁴. TIP5, the largest subunit of NoRC chromatin-remodeling complex, known to silence ribosomal RNA (rRNA) genes by establishing a heterochromatic structure can be acetylated by nicotinamide through inhibition of SIRT1²⁰⁵. Acetylation regulates the interaction of NoRC with promoter-associated RNA (pRNA), which in turn affects heterochromatin formation, nucleosome positioning and rDNA silencing²⁰⁵.

Psammaplin A present in margin sponge inhibits class I HDACs and induces cell cycle arrest and apoptosis^{206, 207}. Baud *et al.* demonstrated that Psammaplin A is a highly potent HDAC1 inhibitor *in vitro* (IC₅₀: 0.9 nM) and can induce acetylation on histones and α -tubulin¹⁶⁴.

Caffeine is a central nervous system (CNS) stimulant of the methylxanthine class found in the seeds, nuts, or leaves of a number of plants, the most well-known source being the coffee plant. In pregnant rats, 120mg/kg/d caffeine reduced expression of a key transcription factor steroidogenic factor-1 (SF-1) in the fetal adrenal. It was found that caffeine treatment increased the mRNA expression of DNA methyltransferase (Dnmt) 1, Dnmt3a, Hdac1, and Hdac2. This correlated with increased methylation and decreased histone acetylation on the SF-1 promoter¹⁶⁶.

2.10 Clinical Significance

In [clinicalTrials.gov](http://clinicaltrials.gov), there are several studies testing HDAC inhibitors and acetylation changes in cancer and other diseases. However, few trials address the role of dietary fat, fiber, cruciferous vegetable intake, or phytochemicals such as resveratrol and SFN on epigenetic endpoints. Resveratrol has been evaluated for its effect on sirtuins in cardiovascular, diabetes and Alzheimer's disease. Sirtuin activity has also been tested in high-fat diet feeding studies in men where high fat has been reported to decrease NAD(+) and sirtuin activity in muscle biopsies, resulting in hyperacetylation of peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC-1 α)²⁰⁸.

The FACT study proposes to test the relationship between dietary fiber intake and colon cell turnover, to identify new molecular targets based on global protein acetylation analysis²⁰⁹. There are also several ongoing studies testing nicotinamide in Friedreich's ataxia, polycystic kidney disease, lung cancer and Alzheimer's disease.

Several studies on broccoli and/or SFN supplementation that evaluate HDAC inhibition have been reported in [clinicalTrials.gov](http://clinicaltrials.gov). One study aims at identifying the distribution of SFN and its metabolites and evaluates HDAC inhibition following broccoli sprout supplementation in subjects at risk for prostate cancer. The study also proposes to investigate the effects on DNA methylation status and proliferation markers in a pre-biopsy setting (Portland VA Medical Center, OR). Another study testing broccoli sprout extract

supplements for treating ductal carcinoma in situ and/or atypical ductal hyperplasia has been completed. Isothiocyanates were detected in urine samples and changes in proliferation (Ki-67) and HDAC activity have been reported in peripheral blood mononuclear cells (PBMCs) of subjects who consumed the supplement as compared to baseline values (OHSU Knight Cancer Institute, OR).

Moreover, a single intake of 68 g broccoli sprouts in human subjects can inhibited HDAC activity in PBMC 3 h and 6 h following consumption¹⁷⁰. More recent studies have confirmed that fresh broccoli sprouts are far more superior in lowering HDAC activity as compared to a broccoli sprout extract (BSE)²¹⁰ or a myrosinase inactivated broccoli supplement²¹¹²¹². However, mature broccoli (200 g) intake has been reported to be ineffective in lowering HDAC activity²¹³. The lowering of HDAC activity by broccoli supplements in humans has been recently reported to activate p21 and long terminal repeats (LTRs)²¹⁴. In addition, consuming BSE or a diet high on cruciferous vegetables reduced HDAC3 expression in circulating PBMCs and colon biopsies (unpublished data). These differential responses likely relate to the concentrations of bioactive ITC metabolites achieved in the circulation or target tissues.

3.0 CONCLUSIONS

HDAC inhibitors continue to be pursued as a promising class of anticancer agents across a broad spectrum of hematologic and solid neoplasms. These inhibitors are associated with diverse phenotypic outcomes, including suppression of cell proliferation, induction of differentiation, and activation of autophagy/apoptosis. In human clinical trials, however, off-target effects and resistance mechanisms have been observed with currently approved pan-HDAC inhibitors. HDAC-selective agents will likely improve therapeutic outcomes, while clarifying the molecular targets, especially the cadre of non-histone proteins affected by changes in acetylation status.

This review article addresses natural compounds, predominantly found in diet that hold great promise in terms of cancer chemoprevention and treatment. These compounds have both advantages and drawbacks as compared to anti-cancer drugs. Dietary phytochemicals tend to be relatively weak HDAC ligands unlike non-dietary compounds such as TSA, although intracellular metabolism can generate more potent HDAC inhibitor intermediates and provide a means of selective toxicity. In this regard, some dietary compounds can be viewed as “prodrugs” with the potential to generate HDAC inhibitor(s) at the appropriate time and place, taking advantage of dysregulated metabolic pathways in cancer cells.

Dietary compounds also work in synergy with pharmacological agents. The combination of anticancer agents and phytochemicals holds great promise as a therapeutic strategy for the future. However, rather than the random, trial-and-error approaches used historically, a rational development of appropriate combinations ideally should be based on mechanistic considerations. For example, green tea polyphenols acting on DNMTs combined with the HDAC inhibition of SFN might account for augmented ER receptor signaling and the inactivation of co-repressor complexes on the *ER* gene promoter²¹⁵. Curcumin mechanisms impacting HATs and HDACs might cooperate with drugs such as valproic acid¹³⁶ or

hydroxamic acids²¹⁶ to activate p38 MAPK-mediated signaling pathways and arrest the growth of human leukemia cells. Similar cooperativity might explain the synergy observed for TSA combined with HDAC inhibitors in Royal jelly¹⁵⁸. Recently, the combination of EGCG and sodium butyrate was shown to efficiently induce *Survivin* expression in colon cancer cells²¹⁷. Further, the combination of selenium compounds and green tea extract showed improved anticancer activity *in vitro* and *in vivo*²¹⁸. These reports likely represent an incomplete view of all such studies in the literature, but they provide illustrative examples for future work on combination treatments through rational design.

Protein acetylation is a reversible post-translational modification that is tightly regulated in various cellular contexts. Acetylomics studies^{10, 219, 220} have identified many differentially acetylated proteins in addition to those summarized in Table 1. However, the role of specific HATs and/or HDACs is far from clear, and the functional significance of acetylation on these proteins requires further investigation. As we begin to define the different sub-categories of non-histone proteins regulated by acetylation, it is becoming apparent that the number of cellular targets implicated is much larger than initially anticipated. Isoform-specific HDAC inhibitors and/or knockdown of selected HDACs, coupled with genome-wide approaches, will likely reveal many new mechanistic targets for therapeutic intervention. These findings will be applied to specific cancer sub-types, as well as in other chronic conditions characterized by altered protein acetylation states and dysregulated gene expression.

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Abbreviations

HDACs	Histone deacetylase
HATs	Histone acetyltransferases
SIRT	Sirtuins
FDA	US Food and Drug Administration
STAT3	Signal transducer and activator of transcription 3
AR	Androgen receptor
COPD	Chronic obstructive pulmonary disease
SCFAs	Short chain fatty acids
TSA	Trichostatin A
βOHB	β-hydroxybutyrate
High-mobility-group	HMG

Estrogen Receptor	ER
GATA	Globin transcription <i>factor</i>
EKLF	Erythroid Kruppel like fator
YY1	Ying Yang 1
Rb	Retinoblastoma protein
HIF 1α	Hypoxia inducible factor
CtIP	C-terminal binding protein interacting protein
Hsp90	Heat Shock Protein 90
FOXO	Forkhead box O
PGC-1α	Peroxisome proliferator-activated receptor- γ coactivator-1 α
GCN5	General control nonderepressible 5
CBP	<i>CREB-binding protein</i>
PCAF	P300/CBP-associated factor
TIP60	Tat interacting protein 60
FXR	<i>Farnesoid X receptor</i>
MSA	Methylseleninic acid
SFN	Sulforaphane
MSP	Methylselenopyruvate
ITCs	Isothiocyanates
allyl-ITC	Allyl isothiocyanate
BITC	Benzyl isothiocyanate
PHITC	Phenylhexyl isothiocyanate
PEITC	Phenethyl isothiocyanate
TRAMP	<i>Tyrosine Rich Acidic Matrix Protein</i>
GSTP1	Glutathione S-transferase gene
I3C	Indole-3-carbinol
DIM	3,3'-diindolylmethane
SEB	Staphylococcal enterotoxin B

PN	Parthenolide
AM	Allyl mercaptan
DADS	Diallyl disulfide
SAC	S-allylcysteine
SAMC	S-allylmercaptocysteine
NAT	N-acetyltransferase
EGCG	Epigallocatechin-3-gallate
NFκB	Nuclear factor kappa B
IL6	Interleukin 6
PcG	Polycomb group
ROS	Reactive oxygen species
SOCS	Suppressor of cytokine signaling
COX-2	Cyclooxygenase-2
pRNA	Promoter-associated RNA
rRNA	Ribosomal RNA
PBMC	Peripheral blood mononuclear cells
BSE	Broccoli sprout extract
LTRs	Long terminal repeats
BMF	Bcl2 modifying factor
SF-1	Steroidogenic factor-1
Dnmt	DNA methyltransferase
PBMCs	Peripheral blood mononuclear cells

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A) Catalytic site binding (Direct)

B) Allosteric site binding (Direct)

C) Complex dissociation (Indirect)

D) Protein turnover/degradation (Indirect)

Fig 1. Mechanisms of HDAC inhibition by dietary compounds

Dietary compounds inhibit HDAC activity and/or expression *via* direct or indirect mechanisms. **(A)** Hydroxamic acids interact with the zinc atom in the catalytic site *via* a bidentate ligand. In dietary compounds such as butyrate, the corresponding interaction likely involves a carboxyl moiety²²¹; whereas in garlic organosulfur compounds, it is the sulfhydryl group of AM²²². **(B)** Allosteric site binding, as predicted for the SFN-NAC metabolite in the inositol tetrphosphate (IP4) pocket that lies between HDAC3 and its corepressor partner SMRT⁹⁴. **(C)** Dissociation of co-repressor complexes due to SFN-mediated CK2 kinase recruitment and HDAC3/SMRT phosphorylation¹⁷². **(D)** Ubiquitylation leading to HDAC3 protein turnover, triggered in cancer cells by dietary indoles¹⁰⁴.

Fig 2. Dietary deacetylase inhibitors and (de)acetylation targets

Deacetylase inhibitors induce histone hyperacetylation leading to an open chromatin conformation that correlates with gene activation. Acetylation of non-histone proteins modulates their function, stability, cellular localization, and/or protein–protein interactions. Transcription factors such as STAT3 and p53 are directly acetylated by HDAC inhibitors, which can positively or negatively alter their capacity to bind DNA and modulate gene expression. Through the combined effects on histone and non-histone protein acetylation, deacetylase inhibitors exert chemopreventive outcomes ranging from inhibition of cell growth, cell cycle arrest, apoptosis, autophagy, or necrosis.

Table 1

Non-histone targets of HATs and HDACs

Non-histone	HAT	HDAC
p53	p300/CBP ^{46, 47}	HDAC1 ⁴⁸ , SIRT1 ⁴⁹
YY1	p300/CBP ⁵⁰	HDAC2 ⁵¹
STAT3	p300/CBP ¹⁷	HDAC3 ¹⁷
HMG	CBP, PCAF ⁵²	NA
c-Myc	PCAF/GCN5, TIP60 ⁵³	NA
AR	p300/CBP, TIP60 ⁵⁴	HDAC1 ⁵⁵
ER	p300 ⁵⁶	NA
GATA	CBP (GATA1) ⁵⁷ , p300 and PCAF (GATA2) ⁵⁸	HDAC3(GATA2) ⁵⁹
EKLF	p300/CBP ⁶⁰	NA
MyoD	PCAF, CBP, and p300 ^{61, 62}	HDAC1 ⁶³
E2F/Rb	PCAF, CBP, and p300 ⁶⁴	HDAC1 ⁶⁵
NF- κ B	p300/CBP ⁶⁶	HDAC3 ⁶⁶ , SIRT1 ⁶⁷
HIF1 α	ARD1 ⁶⁸	HDAC4 ⁶⁹
Smad7	p300 ⁷⁰	
α -Tubulin	NA	HDAC6 ²⁵ , SIRT2 ²³
Importin- α	CBP, p300 ⁷¹	NA
Ku70	PCAF, CBP ⁷²	SIRT1 ⁷²
Hsp90	NA	HDAC6 ⁷³
E1A	p300, PCAF ⁷⁴	NA
CtIP	GCN5 ⁹⁴	HDAC3 ⁹⁴ , SIRT6 ⁷⁵
β -catenin	PCAF ⁷⁶ , p300 ⁷⁷	SIRT1 ⁷⁸ , HDAC6 ⁷⁹
Survivin	NA	HDAC6 ⁸⁰
FoxO1	CBP/p300 ⁸¹	SIRT1 ⁸²
FoxO3a	CBP/p300 ⁸²	SIRT1 ⁸² , SIRT2 ⁸³ , SIRT3 ⁸⁴
PGC1- α	GCN5 ⁸⁵	SIRT1 ^{74, 86}
FXR	p300 ⁸⁷	SIRT1 ⁸⁸

NA: Not available

Table 2

Non-histone target of dietary HDAC inhibitors

Compound	Phytochemical	Chemical structure	HAT/HDAC	Histone	Non-histone	Outcome
Butyric acid	Sodium butyrate		HDAC1 and HDAC3 ³⁴	H3, H4 ³⁴	NA	Inhibition of tumor growth, Apoptosis, Cell cycle arrest
Sulfonamide	Sulfonamide		HDAC1, 2, 3, 4 HDAC7, HDAC6 ⁸⁹⁻⁹²	H3, H4 ⁸⁹⁻⁹²	α -Tubulin ⁹³ , CUP ⁹⁴	Inhibition of tumor growth, Apoptosis, Cell cycle arrest
	Allyl-ITC		HDAC ⁹⁵	H3, H4 ⁹⁵	NA	Inhibition of tumor growth, Apoptosis, Cell cycle arrest
	BITC		HDAC1 and HDAC3 ⁹⁶	H3 ⁹⁶	FoxO1 ⁹⁷	Inhibition of tumor growth, Apoptosis, Cell cycle arrest, Autophagy
	PHITC		HDAC and p300 ⁹⁸ , HDAC1 and HDAC2 ⁹⁹	H3, H4 ⁹⁹⁻¹⁰¹	NA	Apoptosis
Isothiocyanate	PEITC		NA	H3 ¹⁰²	α -Tubulin ¹⁰³	Attenuating cell proliferation, Apoptosis
	I3C		HDACs ¹⁰⁴ HDAC1, HDAC2 ¹⁰⁵ , HDAC3 ^{106, 107}	H3, H4 ¹⁰⁴	NA	Cell cycle arrest, T cell activation
Lactone	Parthenolide		HDAC1 ¹⁰⁸	H3 ¹⁰⁸	NA	Inhibition of tumorigenesis, Apoptosis
Disulfide	Diallyl disulfide		N-acetyltransferase ¹⁰⁹ HDACs	H3, H4 ¹¹⁰⁻¹¹³	NA	Adipocyte differentiation, Apoptosis

Compound	Phytochemical	Chemical structure	HAT/HDAC	Histone	Non-histone	Outcome
	Allyl mercaptan		HDACs ¹¹⁴	H3, H4 ^{95, 114–117}	NA	Inhibition of tumor growth, Apoptosis, Cell cycle arrest
	MSA		HDAC2 and GCN5 ¹¹⁸	H3 ¹¹⁹ H3K18 and H3K9 ¹¹⁸	α -Tubulin ¹¹⁹	Inhibition of tumor growth, Apoptosis, Cell cycle arrest
	Selenite		HDAC ¹²⁰	H3K9 ¹²⁰	NA	Inhibition of tumor growth, Apoptosis, Cell cycle arrest
	MSP		HDAC1 and HDAC8 ¹²¹	H3K9/14, H4 ¹²¹²⁶	NA	Apoptosis
	EGCG		HDAC1, HDAC2, and HDAC3 ¹²²¹²³ HAT ¹²⁴	H3K9/14 H4K5,12,16,H3K9/18 ¹²²¹²⁵¹²⁶	p53 ^{127, 128} FoxO1 ¹²⁹ AR ¹³⁰ Smad2/3 ¹³¹	Inhibition of tumor growth, Apoptosis, Cell cycle arrest
	Curcumin		HDAC1, HDAC2 ¹³² HDAC3 HDAC4 ¹³³ HDAC6 ¹³⁴ HDAC8 ¹³⁵ P300	H3, H4 ¹³⁵¹³⁶ H3K18ac, H4K16ac ¹³⁷	p53 ¹³²¹³⁸	Inhibition of tumor growth, Apoptosis, Cell cycle arrest
	Resveratrol		SIRT1 HDACs ¹³⁹ , SIRT2 ¹⁴⁰	H3, H4 ¹³⁹	p53 ¹⁴¹ , FXR ⁸⁸ , PGC1- α ¹⁴² , FOXO3a ¹⁴³	Inhibition of tumor growth and cell proliferation, Apoptosis, Cell cycle arrest

Compound	Phytochemical	Chemical structure	HAT/HDAC	Histone	Non-histone	Outcome
	Chrysin		HDAC8 ¹⁴⁴	H3acK14, H4acK12, H4acK16 ¹⁴⁴	NA	Cell cycle arrest, Inhibition of proliferation
	Ellagic acid		HDAC6 ¹⁴⁵ , HDAC9 ¹⁴⁶	NA	NA	Inhibition of proliferation, Apoptosis, Cell cycle arrest
	Quercetin		SIRT6 ^{147,148}	H3K56ac ¹⁴⁸	NA	Inhibition of a β -catenin pathway, Inhibition of tumor growth, Apoptosis, Cell cycle arrest
	Apigenin		HDAC1, HDAC3 ¹⁴⁹	H3, H4 ¹⁴⁹	NA	p53 activation, Generation of ROS, apoptosis, Inhibition of tumor invasion, Cell cycle arrest
	Genistein		HAT1 ¹⁵⁰ , HDAC1 ¹⁵¹ , SIRT1 ¹⁵²	H3K9 ^{150, 152} , H3 ¹⁵³ , H4 ¹⁵⁴	NA	Apoptosis, Inhibition of cell proliferation and growth
	Luteolin		CBP/p300 ¹⁵⁵ , SIRT6 ¹⁴⁷	H3, H4 ¹⁵⁶	NA	Apoptosis, Inhibition of invasiveness

Compound	Phytochemical	Chemical structure	HAT/HDAC	Histone	Non-histone	Outcome
	(E)-10-hydroxy-2-decenoic acid (10HDA)		HDAC3 ¹⁵⁷	H3, H4 ¹⁵⁸	NA	Apoptosis, Cell cycle arrest
	Nicotinamide		SIRT1 ¹⁵⁹	H3 ¹⁶⁰	p53 ^{161, 162} , BCL6 ¹⁶³ , BAZ2a, NPM1, MOF, WRN, Ku70 and Ku80 ¹⁶⁰	Cell cycle arrest, Apoptosis
Compound	Psammethin A		HDAC1, HDAC6 ¹⁶⁴ , SIRT1 ¹⁶⁵	H3, H4 ¹⁶⁴	Tubulin ¹⁶⁴	Apoptosis, Inhibition of proliferation, Cell cycle arrest
Alkaloid	Caffeine		Hdac1 and Hdac2 ¹⁶⁶	H3K9 and H3K14 ¹⁶⁶	NA	Fetal development

Downloaded with lysine antibody in the presence of SFN. AR* and Smad2/3* are deacetylated in the presence of EGCG in human lung cancer cells.