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Epigenetic mechanisms of plant-derived anticancer drugs

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1. ABSTRACT

Epigenetic mechanisms are essential for normal development and maintenance of adult life. Disruption of epigenetic processes results in deregulated gene expression and leads to life-threatening diseases, in particular, cancer. Global epigenetic alterations are a hallmark of cancer. Cancer epigenetics revealed the deregulation of all components of the epigenetic machinery including DNA methylation, histone modifications, chromatin structure, and non-coding RNAs. Drugs targeting epigenetic processes, or "epi-drugs", are at the forefront of drug discovery, and plant-derived compounds have shown promise. Most of the plant-derived anticancer drugs that work through epigenetic mechanisms are polyphenols; the others are alkaloids, organosulfur compounds, and terpenoids. This review focuses on the epigenetic machinery and its basis for cancer therapy, highlights plant-derived anticancer drugs with epigenetic mechanisms of action, and discusses their potential use in epigenetic therapy.

2. INTRODUCTION

Until 1970, the DNA sequence was considered to be the only source of genetic information (1). We currently understand that there is an additional layer of information encoded in or around the genome exceeding the information of the genetic sequence. This additional level of information “on or over the DNA” is called epigenetics and is achieved by epigenetic modifications which in their entirety are called the epigenome (2). Epigenetics is defined as “a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" (3). Epigenetic regulation encompasses DNA methylation and histone modification, namely acetylation, methylation, phosphorylation, ubiquitinylation, sumoylation, ADP ribosylation, glycosylation, carbonylation, and biotinylation (4-6). Although DNA methylation and histone acetylation result in repression and activation of gene expression respectively, the other epigenetic modifications have variable effects on gene expression (7). In this review, we focus on the epigenetic mechanisms of DNA methylation, histone acetylation, and microRNAs (miRNAs) and modulation by plant-derived anticancer drugs. For a detailed description of the different types of epigenetic modifications in cancer, we refer the reader to recent reviews (4, 8)

Cancer arises from both, epigenetic and genetic abnormalities, that cause deregulated gene expression and function (9). Epigenetic alterations are reversible, unlike genetic ones, placing epigenetic drugs at the forefront of cancer therapy (4, 10). The most frequent epigenetic changes are increased methylation of CpG (phopshorylated cytosine-guanine) islands within gene promoters and deacetylation or methylation of histones (9-12). Epigenetic mechanisms altering transcription of genes involved in cell differentiation and proliferation are often targets for deregulation in tumor development. In addition to affecting transcription of protein-encoding mRNAs, noncoding miRNAs, which can control the expression of numerous cellular proteins by affecting mRNA stability and/or translation, are similarly part of the epigenome (13-14).

There is evidence that epigenetic deregulation can be a preliminary transforming event (15). Epigenetic changes such as global DNA hypomethylation and promoter-specific hypermethylation are commonly observed in early-stage tumors (16). This suggests that epigenetic alterations are early events in the loss of cellular homeostasis and may precede genetic mutations and genomic instability. Moreover, epigenetic disruptions in tumors are generally of a clonal nature indicating occurrence in early generations of cells. Deregulated epigenetic mechanisms may initiate genetic instability, resulting in the acquisition of genetic mutations that inactivate tumor-suppressor genes and activate oncogenes (17). In addition, DNA hypomethylation often occurs in repetitive DNA sequences in cancer including heterochromatic DNA repeats and dispersed retrotransposons (18). Demethylation of heterochromatic repeats, such as centromeric ones, including chromosomal fragility, and demethylation of retrotransposons causes their reactivation, leading in both cases to chromosomal instability. Therefore, an ideal demethylating therapy preferentially demethylates promoters of tumor suppressor genes, while sparing heterochromatic DNA repeats (17). Fortunately, preferential demethylation is observed with some newly developed demethylating agents. Furthermore, histone deacetylase (HDAC) inhibitors are emerging as promising groups of anticancer agents with targeted epigenetic mode of action (19).

Considering the fact that epigenetic alterations are reversible and repairable, "epi-drugs", which are drugs targeting epigenetic mechanisms (20), show promise in cancer therapy (4, 10). Natural products modulating epigenetic mechanisms constitute part of the hope offered by pharmaco-epigenomics in cancer prevention and treatment (6, 20-22). In particular, many plant-derived anticancer drugs are clinically used as anticancer agents (22-24) and target several tumor pathways including epigenetic ones (25). In this review, we highlight the different plant-derived drugs that work through epigenetic mechanisms in cancer and the promise they offer in epigenetic therapy. Although environmental factors and dietary agents, such as vitamins and minerals influence epigenetic mechanisms (26-27), they are beyond the scope of this review.

3. DNA METHYLATION: MECHANISMS, RELEVANCE TO CANCER, AND MODULATION BY EPI-DRUGS

3.1. DNA methylation and DNA methyltransferases

DNA methylation occurs at cytosines located 5' to a guanosine as part of a CpG dinucleotide. These dinucleotides are frequent in 0.5–4 kb CpG islands in the proximal promoter regions of about half of the genes in our genome, and their methylation results in gene silencing. DNA methylation is accomplished by DNA methyltransferases (DNMTs) which use *S*-adenosyl-L-

methione (SAM) as a methyl group donating cofactor (28). So far, five DNMTs are known in mammals, called DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L. The five enzymes share some structural similarities with a catalytic domain located at the C-terminus end and show differential nuclear localization. For instance, DNMT1 localizes within the replication fork during S phase, whereas DNMT3a and DNMT3b remain diffuse in the nucleus.

DNMT1 is a maintenance DNMT because it copies DNA methylation from the parental strand to the newly synthesized daughter strand. DNMT1 also exhibits some *de novo* methylation activity *in vitro* (29). The biological role of human DNMT2 does not support a role in DNA cytosine methylation, and recent evidence has revealed that human DNMT2 methylates instead aspartic acid transfer RNA ($tRNA^{Asp}$) (30). DNMT3a and DNMT3b are also involved in both, *de novo* and maintenance cytosine methylation; however, their contribution to *de novo* methylation is much higher than DNMT1, which demonstrates a 40-50 fold preference for hemimethylated over un-methylated CpG sites (31). DNMT 3 like protein (DNMT3L) is the third member of the DNMT3 family. DNMT3L acts as a regulatory factor for DNMT3a and induces *de novo* DNA methylation of imprinted genes in mammalian germ cells by recruiting or activating DNMT3a (32-33).

Recently, a new layer of epigenetic modifications, hydroxymethylation on cytosine 5' ends, was identified, whereby a 5-methyl cytosine (5-mc) is converted by TET1, a 2-oxoglutarate- and Fe(II)-dependent enzyme, into a 5-hydroxymethylated form (5-hmc) (34). The role of 5-hmc is still unclear, and 5-hmc is thought to be an intermediate in oxidative demethylation pathways, which result in DNA demethylation. 5-hmc may cause DNA demethylation passively, by interfering with DNMT1 during cell division, or actively if it is replaced by cytosine as part of DNA repair mechanisms (35). 5-hmc may also displace 5-mc-binding proteins from methylated DNA.

3.2. DNA methylation and cancer

Epigenetic therapy at the DNA level focuses on the demethylation of hypermethylated promoter regions of aberrantly silenced tumor suppressor genes in malignant cells (36). However, demethylation is not always selective in reactivating specific target genes but can rather occur across several regions of the genome leading to the reactivation of a random number of genes (6, 37). Such global demethylation patterns result in chromosomal instability but also in a methyl-free DNA scaffold in which a tumor cell is given new opportunities to reestablish normal methylation patterns. The first aberrant epigenetic mechanism in cancer cells is global DNA hypomethylation. Therefore, demethylation-based therapy can aggravate the hypomethylation status in cancer cells making them more susceptible to demethylating agents than normal ones (6) . Examples of genes reactivated by promoter demethylation include *MLH1*, thus, increasing chemosensitivity (38). Similarly, the demethylation and reactivation of *E-cadherin, MYOD*, tumour antigens, *DAPK1*, and *p16* result in cell adhesion (39), induce differentiation (40), increase immunogenicity (41-42), induce apoptosis (43-44), and inhibit uncontrolled cell growth (45-46), respectively.

3.3. Modulators of DNA methyltransferases

Several studies have shown the ability of DNMT inhibitors to prevent or treat cancer through various mechanisms (47-48). Many of these inhibitors are natural products or their synthetic derivatives (49). For example, some disulfide bromotyrosine derivatives, such as psammaplin A, isolated from the sponge *Pseudoceratina purpurea*, were found to be potent inhibitors of DNMT1 but also of HDACs (50). Several plant-derived anticancer drugs extracted from green tea, soybean, coca plant, feverfew, and coffee are modulators of DNA methylation and will be covered later. Most commonly used DNMT inhibitors that are in clinical trials are nucleoside analogues namely 5-azacytidine and 5-aza-2'-deoxycytidine (48). Importantly, non-nucleoside analogs have some advantages over nucleoside analogs as inhibitors of DNA methylation as the latter ones are more cytotoxic. The cytotoxicity of nucleoside analogues is due to their ability to trap DNMTs and not to the resultant demethylation effects (51). As embryonic stem cells and some cancer cells express low levels of DNMTs, they are resistant to nucleoside analogue cytotoxicity. A possible implication of chronic administration of nucleoside analogues is genome-wide hypomethylation with consequent chromosomal instability and/or oncogene hypomethylation with consequent activation. Hypomethylation of *c-Myc and c-Jun* protooncogenes is observed in livers of mice exposed to hypomethylating diets (52). Therefore, direct inhibition of specific DNMTs is an ideal strategy for reversal of silenced hypermethylated genes and evades the drawbacks of the nucleoside analogues' nonspecific cytotoxic effects (48). Natural products can specifically target DNMTs and, hence, may often be preferable to nucleoside analogues.

4. HISTONE MODIFICATIONS: MECHANISMS, RELEVANCE TO CANCER, AND MODULATION BY EPI-DRUGS

Histones have amino-terminal tails protruding out of the nucleosomes. These tails are subject to post-translational modifications, such as acetylation and methylation of lysines and arginines, phosphorylation of serines and threonines, sumoylation, ubiquitinylation and biotinylation of lysines, and ADP ribosylation, glycosylation, and carbonylation (5, 53-54). Epigenetic crosstalks exist between DNA methylation and histone modifications (55). For instance, DNMTs can recruit HDACs (55); therefore, it is not surprising that the combination of DNMT and HDAC inhibition can induce differentiation and cell death in several cancer cells (56) in a synergistic manner (49).

Histone post-translational modifications can have variable effects on gene expression. In general, acetylation of certain lysine residues by histone acetyltransferases (HATs) is associated with transcriptionally active regions, whereas transcriptionally repressed chromatin is usually

hypoacetylated (57). On the other hand, methylation of lysine residues leads either to transcriptional activation or repression, depending on the site of lysine methylation (58). Since there are different states of methylation (mono-, di- or trimethylation) possible for one lysine residue, the biological consequences of methylation may differ (59). Interestingly, certain histone modifications namely, trimethylation of histone H4 and global loss of monoacetylation are common in human cancers (60). In addition, phosphorylated H3Thr11 correlates with Gleason scores of prostate carcinomas (61).

4.1. Histone acetylation

4.1.1. Histone acetyl transferases and histone deacetylases

Allfrey *et al.*, were the first to suggest that acetylation of histones is involved in regulation of transcription (62). HAT enzymes can be classified into several groups, including the GNAT family (e. g., GCN5, PCAF), the MYST group (e. g., Tip60), the p300/CBP family, the SRC group, and the TAFII250 family (63). The HDACs can be divided into four classes (64). Class I HDACs include HDAC1, HDAC2, HDAC3, and HDAC8 and are primarily located in the nucleus, where they interact with transcriptional repressors and cofactors (64-65). Class II HDACs include HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10 and its members are able to shuttle between the cytoplasm and the nucleus (64). Interestingly, one of these deacetylases, HDAC6 has two catalytic domains, one for histone deacetylation, and one for deacetylation of tubulin (66), showing that HDACs, as well as HATs, can also target non-histone protein substrates. The HDACs of classes I, II and IV have a zinc ion at the base of their catalytic pocket and a hydrophobic pocket that allows the acetylated lysine residue to insert. The third class of HDACs is called Sirtuins after their homology to the yeast silent information regulator 2 (Sir2) (67). The latter HDACs differ from the zinc-dependent HDACs of classes I, II, and IV in that they are dependent on nicotinamine adenine dinucleotide (NAD^+) instead. For class III HDACs, also a large number of non-histone substrates, such as p53 and tubulin have been reported (68-70).

4.1.2. Modulators of histone deacetylases

The HDAC inhibitors are classified into different groups depending on their structure, including small-chain fatty acids, hydroxamic acids, cyclic tetrapeptides, benzamides, and others (71-73). The first inhibitors of HDAC classes I and II were isolated from natural sources upon which a variety of synthetic inhibitors have been developed (73).

The largest group of HDAC inhibitors is that of compounds carrying a hydroxamic acid as the zinc binding group (ZBG) with the natural product trichostatin A (TSA) as lead structure. TSA, isolated from *Streptomyces hygroscopicus* and currently in clinical trials, inhibits HDACs of group I and group II in the nanomolar range and induces differentiation, cell cycle arrest, and apoptosis (74). Other HDAC inhibitors are in clinical trials and have shown potential against different kinds of tumors (73, 75-76). Among them is the natural product FK-228 (also known as FR-90 122 or depsipeptide), which is in clinical trials for the treatment of chronic lymphocytic leukemia, acute myelogenous leukemia, and T-cell lymphoma (77). Another drug in clinical trials is butyrate, a short-chain fatty acid which inhibits HDAC activity at high micromolar concentrations, is formed in the digestive tract by fermentation of dietary fiber. Although therapeutic intervention with butyrate is not promising, a continuous exposure, stemming from the microbial degradation of dietary fiber in the colon, could have chemopreventive effects, at least in part, by HDAC inhibition (78). Moreover, ester prodrugs of butyrates have shown promise in colorectal cancer treatment (79). Numerous other HDAC inhibitors are in clinical trials and are listed elsewhere (6, 8, 80). Several plant-derived anticancer drugs that work through epigenetic mechanisms were extracted from apple of cashew, turmeric spice, grapes, cruciferous vegetables, garlic, and onion and were shown to modulate histone acetylation as will be covered later.

Strikingly, tumor cells seem to be more sensitive to the actions of HDAC inhibitors than normal cells. The mechanisms behind this cancer selectivity are not fully understood, but it has been reported that thioredoxin, the intracellular thiol status and the accumulation of reactive oxygen species (ROS) as well as the induction of TRAIL, DR4 and DR5 may be involved (81-82). Moreover, HDACs interact directly with the tumor suppressor protein p53 by removing acetyl groups from its C-terminal tail, resulting in decreased transactivation. HDAC inhibitors can cause an increase in p53 acetylation, leading to its activation which could sentence a cell with DNA abnormality to death (72).

Prior to metastasis, a primary tumor requires vascularization to supply nutrients and oxygen. Hypoxia, one of the factors inducing angiogenesis, is known to increase HDAC1 expression levels and activity (83), and abrogation of HDAC1 was shown to inhibit angiogenesis *in vitro* and *in vivo* (84). Another pathway leading to cancer metastasis is the up-regulation of stimulatory factors of the immune system. HDAC inhibition induces expression of CD40, CD80, and CD86, as well as major histocompatibility proteins of class I and class II and interferons (72), thus, making it difficult for tumor cells to survive (49).

Global genomic approaches demonstrate that HDAC inhibitors regulate the expression of a small (~2%) set of genes (85). Additionally, HDAC inhibitors induce hyperacetylation of non-histone proteins such as NF-κB (86), p53 (87), and Hsp90 (88). Hyperacetylation of both histones and non-histone proteins by HDAC inhibitors indicate that these compounds are in fact "lysine deacetylase" inhibitors and not just HDAC inhibitors. Interestingly, hyperacetylation of non-histone proteins like Hsp90 by HDAC inhibitors induces DNMT1 protein downregulation by promoting the ubiquitin-dependent proteasomal degradation of DNMT1 (89), highlighting an indirect effect of HDAC inhibitors on the DNA methylation machinery (48, 55).

4.1.3. Modulators of histone acetyl transferases

Direct cancer chemoprevention and treatment by specific modulators of HATs (90) is not as common as the use of HDAC inhibitors (91-92). In fact, none of the HAT inhibitors has advanced into cancer clinical trials yet (48). However, HATs are currently emerging as drug targets and have been implicated in several diseases, including cancer, and viral infections, resulting in the development of specific HAT inhibitor drugs (90). Several plant-derived anticancer drugs such as anachardic acid, curcumin, (-)-epigallo-catechin-3-gallate (EGCG), garcinol, sanguinarine, and S –allylmercaptocysteine are HAT inhibitors and will be described later. Synthetic HAT inhibitors include bisubstrate inhibitors, α-methylene-γ-butyrolactone inhibitors, and isothiazolones (90). The bisubstrate inhibitors show selectivity for PCAF and p300 inhibition, the α-methylene-γ-butyrolactone inhibitors target GCN5, and the isothiazolones inhibit PCAF (90).

4.1.4. The histone acetyl transferase – histone deacetylase balance

It has been suggested that modulation of HAT or HDAC activity in any direction might induce differentiation and senescence in tumor cells (93-94). One reason may be that histone acetylation status is a common endpoint which tilts cellular homeostasis through modulation of HATs, HDACs, or both. Moreover, in addition to tissue-specific effects of histone acetylation (20), site-specific histone acetylation in the chromatin is as important in regulating gene expression and is a property of numerous plant-derived epi-drugs. In fact, an ideal anticancer epi-drug can promote histone acetylation to activate tumor suppressor genes and deacetylation to inhibit oncogenes in order to efficiently suppress tumorigenesis. Up to 20% of all known genes are regulated by HDAC inhibition with approximately half of them being upregulated, and the other half downregulated (95). Another reason is that the acetylation of nonhistone targets can be also regulated by HAT/HDAC inhibitors causing alterations beyond protein-DNA interactions to include enzyme activities and protein–protein interactions, hence, effecting more complex signal transduction pathways (96). Hence, deregulation of the protein acetylation-deacetylation balance (94), and the "chaotic disequilibrium" between genetic and epigenetic mechanisms drives tumorigenesis (20). It is currently hard to predict universal cellular targets responsible for HDAC inhibition-mediated effects. The development of isoform-selective HDAC inhibitors provides experimental tools to further understand the complex biology of theses enzymes and to dissect their diverse cellular targets (97). Luckily, normal cells show reduced sensitivity to treatment with HDAC inhibitors, pinpointing to huge differences in the acetylome in normal *versus* cancer cells that are waiting to be unraveled (95).

4.2. Histone methylation

4.2.1. Methylation at arginine residues

The methylation of arginine residues contributes to transcriptionally repressed but mostly to transcriptionally active genes and is catalyzed by protein arginine methyltransferases (PRMTs) (98-100). Arginine methylation can occur in three different states, monomethylated, symmetrically dimethylated, or asymmetrically dimethylated (101). In mammals, PRMT1 and PRMT4 catalyze asymmetric dimethylation causing gene activation while PRMT5 induces symmetric dimethylation leading to gene repression. PADI4, a peptidyldeiminase, is able to remove methyl groups from methylated arginines leading to citrulline (101-102) and causing transcriptional repression. Jumanji domain-containing protein 6 (JMJD6) was thought to remove methyl groups from dimethylated arginines (103) but is no longer considered an arginine demethylase but rather a lysine hydroxylase (104).

4.2.2. Methylation at lysine residues

The methylation of lysine residues can lead either to activation or repression of gene expression, depending on the particular histone lysine residue (58). Methylation of H3Lys4, H3Lys36, and H3Lys79 result in transcriptional activation (105), whereas methylation of H3Lys9, H3Lys27, and H4Lys20 are associated with transcriptional repression (106). The methylation state (mono-, di- or trimethylation) is variable and affects differentially transcription (59). Histone lysine methylation is achieved by a family of proteins containing a SET (suppressor of variegation, enhancer of zeste and trithorax) domain and by the non-SET-domain proteins DOT1/DOT1 L (107-108). All lysine methyltransferases use SAM as the cofactor. Until recently, it was assumed that histone lysine methylation was an irreversible process (49). Then the lysine specific demethylase 1 (LSD1), known as a component of several HDAC complexes, was identified as an amine oxidase which selectively removes methyl groups from H3Lys4 (mono- or dimethylated) (109). LSD1 is not able to demethylate trimethylated lysine residues, however, JMJD enzymes are able to demethylate trimethylated lysine residues in an oxidation reaction also dependent on Fe(II) and α-ketoglutarate (49).

4.2.3. Modulators of histone demethylases

So far, only few small molecule modulators of the histone lysine demethylating enzymes have been described. But evidence suggests that LSD1, which shares homology with monoamine oxidases (MAOs), is a promising target in both cancer prevention and therapy (49). Examples of LSD1 inhibitors include the MAO inhibitor, Pargyline (110), among others (111). LSD1 is up-regulated in mammary tumor formation in epithelial cells that have been exposed to dietary and environmental carcinogens (112), and serves as a biomarker predictive for aggressive prostate cancer (113) . Importantly, inhibition of LSD1 in colon carcinoma cells results in re-expression of tumor suppressor genes that are lost in colon cancer (114). The colocalization of LSD1 and the androgen receptor (AR) in androgen-dependent tissue is due to the fact that LSD1 stimulates AR-dependent transcription (115). JMJD2C, a member of the JMJD enzymes, was shown to regulate the AR as well. It was found that JMJD2C colocalizes with LSD1 and the AR, and that both demethylases cooperatively stimulate AR-dependent gene expression (116).

4.3. Histone phosphorylation

Histone phosphorylation may occur on any histone, and phosphorylations at H3Thr3, H3Ser10,

H3Ser28, and H2AThr119 correlate with cell cycle progression during cell division and with gene activation during interphase (117-120). During mitosis, Aurora kinases (Aurora A, B, and C) phosphorylate H3, nucleosomal histone kinase-1 phosphorylates H2AThr119 (118, 121-123), and the kinase haspin is essential for mitotic H3Thr3 phosphorylation and for chromosome alignment in metaphase (119). Importantly, Aurora kinases are overexpressed in many types of human tumors, and H3 phosphorylation is crucial for malignant transformation (124). As for protein phosphatases (PPs), PP1 and PP2A are likely to be associated with dephosphorylation of H2A and H3 (125-128).

4.3.1. Modulators of histone kinases

The screening of approximately 250,000 compounds for inhibition of human Aurora A kinase provided a lead compound which was further modified to produce ZM447439 (129). This compound specifically inhibits Aurora A and Aurora B but not the other assayed protein kinases. It blocked chromosome condensation, mitotic spindle assembly, and the spindle integrity checkpoint (130). Another molecule, Hesperadin, was shown to inhibit the catalytic activity of Aurora B. Treatment of breast and colon cancer cells with hesperadin inhibited proliferation due to multiple mitotic defects caused by a reduction in Aurora B activity (131-132).

4.3.2. Modulators of histone phosphatases

The natural products okadaic acid, fostriecin, and microcystin LR are specific inhibitors of PP1 and PP2A and stimulate histone H3 phosphorylation. Experiments using these inhibitors have shown that H3 phosphorylation has an intimate involvement in chromosomal condensation and the transcriptional activation of heat shock genes (125-128).

4.4. Other types of histone modifications

Most histone modifications were initially identified on the histone amino-terminal tails which protrude outward from the nucleosomal core histones (133). However, novel histone modifications have been discovered in the core region of histones where histone carboxy-terminals make up the scaffold. One such histone mark is ubiquitinylation that occurs on lysine residues of the carboxy-terminals of histones H2A and H2B. H2B ubiquitinylation, occuring throughout eukaryotic organisms, is unlike the commonly known poly-ubiquitinylation that targets proteins to proteasomal degradation. Instead, a single ubiquitin is added to H2B in a reversible mechanism which affects chromatin structure and gene expression (133). H2B-conjugated mono-ubiquitin can be excised by ubiquitin specific-proteases (133) and is critical to mitotic and meiotic growth, but whether it is involved in transcription is yet to be uncovered (134). Unlike ubiquitinylation, which often has a role in protein degradation, addition of small ubiquitin-related modifier (SUMO) does not (135). Histone sumoylation also occurs on lysine residues and induces gene silencing by recruiting HDAC and heterochromatin protein 1 (135-136).

Biotinylation is another type of histone modification also occurring on histone lysine residues and is catalyzed by biotinidase and holocarboxylase synthetase (137). Lysines 4, 9, and 18 in H3 and lysines 8 and 12 in H4 have been identified as biotinylation sites (5, 137). Global histone biotinylation may positively correlate with increases in cell proliferation, gene silencing (eg. transposable element silencing), and DNA damage (138-139). H4Lys12 biotinylation, however, decreases with DNA double-strand breaks. Whether histone biotinylation leads to DNA repair or apoptosis is yet to be determined (138).

5. RNA INTERFERENCE AND MICRO RNA IN CANCER

RNA interference (RNAi), in which small double stranded RNA (dsRNA) fragments silence the expression of a matching gene, is involved in the regulation of crucial processes in development and adult life (140). RNAi is one of the hottest breakthroughs in biomedical research and has shown promise in cancer therapy where several strategies are being developed through modulation of its functional derivatives small interfering RNAs (siRNA) and miRNAs (141). miRNAs are small (18 to 25) nucleotides encoded and processed from endogenous genes, matured by the RNase Dicer/Drosha from hairpin precursors, and are major players of RNAi (142). miRNAs regulate crucial signaling networks that ensure cellular homeostasis, and their deregulation contributes to cancer development, metastasis, and abnormal stem cell biology (143-144).

Aberrant expression of miRNAs is due to several abnormalities ranging from genetic to epigenetic mechanisms (145). miRNAs control, and are regulated by, epigenetic mechanisms. DNMTs 1, 3a, and 3b are predicted miRNA targets (146) and miRNA-140 targets HDAC4 (147). DNA methylation and histone modifications can affect miRNA expression as miRNA-127, among other miRNAs, are expressed after treatment with 5-Aza-CdR, a DNMT inhibitor, and 4-phenylbutyric acid, an HDAC inhibitor (148). Many miRNAs are encoded by intronic regions under the control of the promoter of a host gene. However, CpG islands within introns encoding miRNAs have been identified and can act as promoters that are regulated by DNA methylation (149-150). Interestingly, information carried by RNA molecules can be inherited across generations as evidenced by the existence of a genome-wide library of stable, heritable RNAs that can serve as templates in DNA repair mechanisms (151).

Several miRNA-based therapeutic strategies are in development and rely on *de novo* programming of the RNAi machinery, targeting specific mRNAs, and sequence-specific inhibition of miRNA functions (141). Recently, some plant-derived compounds, such as curcumin, have emerged as epigenetic modulators of miRNAs (152). miRNA-based therapeutics is function of whether the deregulated miRNA is an oncogene or a tumor suppressor gene (153). miRNAs are potential oncogenes if their amplification or overexpression reduces tumor suppressor genes and contributes to tumor development by enhancing proliferation, angiogenesis, and metastasis. In contrast,

miRNAs are tumor suppressors if they reduce the function of oncogenes and decrease proliferation and metastasis and promote differentiation and cell death (152).

6. PLANT-DERIVED ANTICANCER DRUGS WITH EPIGENETIC ACTIVITIES

Plant-derived anticancer drugs with epigenetic tumor inhibitory mechanisms were divided into major (Table 1) and minor (Table 2) groups based on the number of publications and the variety of targeted cancers. Within each group, the anticancer drugs were categorized based on the class of plant secondary metabolites they belong to. Most of the major plant-derived compounds are in cancer clinical trials, namely, curcumin, which entered Phase III, EGCG, genistein, resveratrol, sulforaphane, and parthenolide (154-157). Among the minor plant-derived compounds, lycopene and thymoquinone are in cancer clinical trials (154, 158). Garlic, from which allyl sulphur compounds are derived, is also in cancer clinical trials (154). Tables 1 and 2 indicate whether the epigenetic mechanisms of plant-derived molecules are based on cell-free biochemical assays, cancer cell lines, and/or *in vivo* animal models.

6.1. Major plant-derived anticancer drugs as epigenetic modulators

Most of the major plant-derived anticancer drugs that work through epigenetic mechanisms are polyphenols; the others are alkaloids, organosulfur compounds, or terpenoids (Figure 1; Table 1).

6.1.1. Polyphenols

Polyphenols are plant secondary metabolites consisting of one or more (poly-) phenol unit(s) (Figure 1; phenol unit shown in red). Their conjugated systems, and hence, electron delocalization properties enable them to efficiently quench free radicals (159). Additionally, phenols bear several hydroxyl groups making them excellent hydrogen bond donors which bind with high affinity to proteins and nucleic acids. Flavonoids are the largest and best characterized polyphenols and include the flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavonoids (160). In general, phenols possess preventive activities in cardiovascular diseases, cancers, osteoporosis, neurodegenerative diseases, and diabetes mellitus (161). Several polyphenolics mediate their anticancer activities by modulating the acetylation pattern of crucial genes and inhibiting hypermethylation of tumor suppressor genes, which is a landmark in cancer development (162).

6.1.1.1. Anacardic acid and derivatives

Anacardic acids are plant phenols extracted from traditional medicinal plants predominantly belonging to the *Anacardiaceae* family and have been shown to exhibit anti-tumor (163-165), anti-oxidant, (166) and anti-microbial activities (167). Anacardic acids differ in their alkyl side chain (R) which may be saturated or unsaturated (Figure 1). Anacardic acid and analogues, such as benzamide derivatives, act as epigenetic modulators by inhibiting the HATs, p300, PCAF, and TBP interacting protein (TIP60) in cervical, breast, kidney, and prostate cancer cells and in lymphoid and myeloid leukemia cells (168-173). Anacardic acid decreased TNF-induced HAT activity in lymphoid leukemia and immortalized kidney cells and caused a p300-dependent p65 hypo-acetylation and NF-κB inhibition (172). In cervical and kidney tumor cells, anacardic acid inhibited Tip60-dependent activation of ataxia-telangiectasia-mutated (ATM) and DNA-protein kinases C (PKCs), thus, increasing cell sensitivity to DNA damage in response to ionizing radiation (169). Although anacardic acid and its derivatives are general HAT inhibitors, one derivative, *N*-(4-chloro-3-trifluoromethyl-phenyl)-2-ethoxy-6-pentadecyl-benzamide (CTPB), enhances p300 HAT activity (168). Such compounds could serve as useful tools for switching p300 activity and providing deeper insights onto the role of p300 in cancer therapy.

6.1.1.2. Curcumin

Curcumin or diferuloylmethane is a naturally occurring flavonoid derived from the rhizome of *Curcuma longa* (152). Oral curcumin is poorly absorbed but shows clinical safety and tolerability at high doses (174-176). Moreover, liposome-encapsulated curcumin can be intravenously administered and shows antitumor effects in various cancer animal models (177-179). Curcumin epigenetically inhibits cancer through modulation of histone acetylation by altering the activities of both, HATs and HDACs (152). Curcumin induces HDAC1 (180) and HDAC2 (181) or inhibits HAT activity leading to a decrease in global and in H3 and H4 histone acetylation in prostate (182), liver (183), brain (184), and Raji lymphoid leukemia cancer cells (180, 185). Interestingly, curcumin specifically inhibited p300/CBP in prostate cancer (182) and lymphoid leukemia cells (180). The inhibition of p300/CBP did not affect other HATs, such as PCAF or GCN5, when histone H3 or p53 were used as substrates (182). Interestingly, acetylation of p53 was shown to have variable effects in cancer development (186). Although curcumin can induce HDAC1, in myeloid leukemia and liver cancer cells, it can also inhibit this enzyme, in addition to HDAC3 and HDAC8, leading to an increase in H3 and H4 acetylation and *p21* expression (180, 185, 187-189).

New roles for curcumin were recently highlighted showing its regulatory effects on miRNAs (190-191) and DNMT1 (192). Curcumin inhibited *miRNA-199a* and induced *miRNA-22* in pancreatic cancer cells leading to suppression of miRNA-22 target genes, namely, the *SP1* transcription factor involved in tumor growth and metastases and the *ER1* gene considered as one of the major therapeutic targets in breast cancer (190). In pancreatic cancer cells, curcumin induced miRNA-200 and inhibited miRNA-21 leading to upregulation of *PTEN*, a miRNA-21 target and tumor suppressor gene (191). The decreased expression of miR-200 and increased expression of miRNA-21 form a signature for tumor malignancy, are the causes for gemcitabine-resistance in cancer, and are both reversed by curcumin (191). Finally, an emerging role for curcumin is inhibition of DNMT1 (192). Curcumin covalently blocked the catalytic thiolate of C1226 of

Table 1. Major plant-derived anticancer drugs as epigenetic modulators

Purified Plant Compound	Plant Origin	Cancer System	Epigenetic Mechanism[1]	References
Polyphenols				
Anacardic acid and derivatives	*Anacardium occidentale* (Apple of cashew)	Cervical (HeLa), embryonic kidney (HEK 293T)	Inhibit Tip60 and Tip60-dependent activation of ATM and DNA–PKCs	169
		Myeloid leukemia (KBM-5), embryonic kidney (HEKA293)	Inhibit TNF-induced HAT activity; decrease p65 acetylation; inhibit NF-kB	172
		Cervical (HeLa)	Inhibit p300	173
		Lymphoid leukemia (Jurkat), cervical (HeLa), prostate (PC-3), breast (MCF-7)	Inhibit HAT activity and p300; decrease H4 acetylation	170
		Embryonic kidney (HEK293), breast (MCF-7)	Inhibit p300; decrease histone acetylation	171
		Cervical (HeLa)[2]	Inhibit p300 and PCAF activities; CTPB derivative induces p300 activity	168
Curcumin and derivatives	*Curcuma longa* (Turmeric spice)	Lymphoid leukemia (Raji)	Induce HDAC1	180
		Lymphoid leukemia (Raji)	Inhibit HDAC1, HDAC3, and HDAC8; increase H4 acetylation	187
		Liver (HepG2)	Inhibit HDAC1	189
		Leukemic monocyte lymphoma (U937)	Induce HDAC2	181
		Prostate (PC-3)	Inhibit p300/CPB; decrease H3 and p53 acetylation	182
		Liver (Hep3B)	Inhibit HAT activity; decrease global histone acetylation and H3 and H4 acetylation	183
		Brain cancer cells & brain-derived neural stem cells	Inhibit HAT; decrease H3 and H4 acetylation	184
		Lymphoid leukemia (Raji)	Inhibit p300, HDAC1, and HDAC3	185
			Inhibit p300 and HDAC1	180
			Increase H3 acetylation at *p21* promoter; induce *p21*	188
		Pancreatic (BxPC-3)	Induce *miR-22*; inhibit *miR-199a* ; inhibit *SP1* and *ER1*	190
		Pancreatic (MIAPaCa-E, MIAPaCa-M,. BxPC-3)	Induce miR-200; inhibit miR-21; induce *PTEN*	191
		Lymphoid leukemia (MV4-11)	Inhibit DNMT1; induce global DNA hypomethylation	192
(-)-Epigallo-catechin 3-gallate	*Camellia sinensis* (Green tea)	UVB skin carcinogenesis mouse model	Decreases UVB-induced global DNA hypomethylation	197
		Colon (HT-29), esophageal/oral (KYSE 510), prostate (PC3)	Inhibits DNMT1 activity; decreases *RARβ, MGMT, p16*, and *hMLH1* promoter methylation; induces these genes	198-199
		Breast (MCF-7, MDA-MB-231, T47-D)	Inhibits DNMT1[2]; decreases *RARβ* promoter methylation	267
		Colon (Caco-2)	Decreases *p16* promoter methylation; induces *p16*	202
		Lung (H460, A549)	Decreases *WIF-1* promoter methylation; induces *WIF-1*	200
		Esophageal/oral (HSC3, HSC4, SCC9, SCC25)	Decreases *RECK* promoter methylation; induces *RECK*	203
		Breast (MCF-7)	Decreases *hTERT* promoter methylation; enhances binding of E2F-1 *hTERT* inhibitor; decreases H3Lys9 acetylation; inhibits *hTERT*	204
		Cervical (HeLa)[2], embryonic kidney (HEK293), myeloid leukemia (THP-1), TNFα mouse inflammation model	Inhibits p300/CBP, PCAF and TIP60; inhibits p300-induced p65 acetylation and binding of p300 to IL-6 promoter; recruits HDAC3 to *IL-6* promoter; inhibits *IL-6*	205
		Epidermal (A431, HaCaT, SCC-13)	Inhibits Ezh2, Suz12 and Bmi-1; decreases global tri-methyl H3Lys27; inhibits CDK1, CDK2, CDK4, cyclin D1, cyclin E, cyclin A, cyclin B1 and Bcl-x_L ; induces p21, p27 and Bax	206

		Liver (HepG2)	Induces *miR-16*; inhibits *Bcl-2*	207
Genistein	*Glycine max* (Soybean)	Esophageal/oral (KYSE 510, KYSE 150), prostate (LNCaP, PC-3)	Inhibits DNMT activity and DNMT1; decreases *RARβ, p16*, and *MGMT* promoter methylation; induces these genes	199, 212
		Breast (MCF10AT, MCF-7)	Inhibits DNMT1, DNMT3a, and DNMT3b; decreases *hTERT* promoter methylation; enhances binding of E2F-1 *hTERT* inhibitor; increases trimethyl-H3Lys9 and decreases dimethyl-H3Lys4 on *hTERT* promoter; inhibits *hTERT*	209
		Myeloid leukemia (HL-60)	Decreases *p57* promoter methylation; induces *p57*	214
		Breast (MDA-MB-468)	Decreases *GSTP1* promoter methylation; induces *GSTP1*	215
		Kidney (A498, ACHN, HEK-293)	Inhibits DNMT activity; decreases *BTG3* promoter methylation; induces HAT activity; inhibits HDAC activity; increases H3, H4, di-methyl H3Lys4, and tri-methyl H3Lys4 acetylation at *BTG3* promoter; induces *BTG3*	210
		Prostate (LNCaP, PC3)	Inhibits DNMT and methyl-binding domain protein 2 activities; inhibits DNMTs 1, 3a, and 3b; decreases *BTG3* promoter methylation; induces HAT activity; increases H3, H4, di-methyl H3Lys4, and tri-methyl H3Lys4 acetylation at *BTG3* promoter; induces *BTG3*	211
			Inhibits SIRT1; demethylates and acetylates H3Lys9 at *PTEN* and *CYLD* promoters; acetylates H3Lys9 at *p53* and *FOXO3a* promoters; induces all these genes	216
		Prostate (LNCaP)	Inhibits HDAC6-Hsp90 interaction; destabilizes androgen receptor	218
		Prostate (LnCaP, DuPRO, RWPE)	Induces *p300, PCAF, CREBBP*, and *HAT1* expression; increases acetylation of H3, H4, and H3Lys4 at the *p16* and *p21* promoters; induces *p16* and *p21*	217
		Breast (MCF-7)	Decreases H3 acetylation	219
		Uveal melanoma cell line	Inhibits miR-27a and *ZBTB10*	220
		Prostate (PC3, LNCaP)	Inhibits all MCM genes; induces miR-1296; inhibits *MCM2*	221
		Ovarian (UL-3A, UL-3B)	Induces 53 miRNAs; induces ERα and ERβ	222
Resveratrol and derivatives	*Vitis vinefera* (Grapes)	Primary BRCA1 mutant and wild-type breast cancer cells, breast cancer xenograft	Induce SIRT1 activity; inhibit *Survivin*	226
		SIRT1-mutant mouse model	Induce SIRT1 downstream genes *G6pase, Pepck*, and *Pgc-1α*	227
		Mouse two-stage skin carcinogenesis model	Decrease tumorigenesis in SIRT1-partially dependent manner	229
		Breast (MCF-7)	Decrease H4 acetylation on *COX-2* promoter; inhibit *COX-2*	233
		Breast (MDA-MB-231, MCF-7), MDA-MB-231 mouse xenograft	Induce SIRT1; induce AMPK	231
		Breast (MCF-7)	Induce SIRT1 activity and SIRT1-p300 association; inhibit p300 activity and p300-induced acetylation of β-catenin and NF-kB-p65; inhibit *MDR1* and *Bcl-x_L*	228
		Lung (NCI-H358, NCI-H460, NCI-H1299), embryonic kidney (HEK 293, HEK 293T)	Induce sirtuin activity; decrease chromatin associated p300 and p300-induced acetylation of RelA/p65; inhibit NF-kB; decrease H3Lys14 acetylation; inhibit recruitment of RNA polymerase II to chromatin	230
		Embryonic kidney (HEK 293), cervical (HeLa)	Induce SIRT1 activity; inhibit p300-induced APE1 acetylation; induces activity and binding of APE1 to XRCC1	232
		Prostate (DU145, LNCaP)	Inhibit MTA1; destabilize MTA1/HDAC1/p53 complexes; increase p53 acetylation; induce *p53* and its target genes *p21* and *bax*	235
Alkaloids				
Procainamide and derivatives	*Erythroxylum coca* (Coca plant)	Lymphoid leukemia (Jurkat)	Inhibit DNMT activity	241
		Colon (HCT116), breast (MCF-7)	Inhibit DNMT1, decrease CpG methylation at alphoid satellite sequences from chromosomes 1 and 18	240
		Breast (MCF-7)	Bind GC-rich DNA; decrease global DNA methylation; decrease *RARβ2* promoter methylation; induce *RARβ2*	245
		Prostate (LNCaP PCA), LNCap PCA mice xenografts	Decrease *GSTP1* promoter methylation; induce *GSTP1*	242
		Breast (MDA-MB-231, MCF-7), bladder (T24), MDA-231 mice xenografts	Decrease *ER, RARβ*, and *p16* promoter methylation; induce these genes	243

		Lung (H460 and A549)	Decrease *WIF-1* promoter methylation; induce *WIF-1*	244
		Cadmium-transformed prostate RWPE-1 epithelial cells	Inhibit cadmium-induced genomic hypermethylation	246
Organosulfur compounds				
Sulforaphane	Cruciferous vegetables	Embryonic kidney (HEK 293), Colon (HCT116)	Decreases HDAC activity; increases global H3 and H4 acetylation; increases H4 acetylation at *p21* promoter; induces *p21*	250
		Prostate (BPH-1, LnCaP, PC-3)	Decreases HDAC activity; increases H3 and H4 acetylation; increases H4 acetylation at *p21* and *bax* promoters; induces *p21* and *bax*	251
		Apc^{min} intestinal mouse model	Decreases HDAC activity; increases total H3 and H4 acetylation at *p21* and *bax* promoters; induces *p21* and *bax*	252
		Prostate (PC-3), PC-3 mice xenografts	Decreases HDAC activity, increases H3 and H4 acetylation; induces *bax*	253
		Prostate (LNCaP , VCaP)	Inhibits HDAC6; increases HSP90 acetylation; inhibits *ERG*	254
Terpenoids				
Parthenolide	*Tanacetum parthenium* (Feverfew)	Breast (ZR-75-1), brain (M059K), sarcoma (GK41-U2OS)	Inhibits HDAC1; increases global H3 acetylation; induces *p21*	258
		Colon (HCT-115), breast (MDA-MB-231)	Inhibits HDAC1	259
		Breast (ZR-75-1), colon (HCT116, HCT116 p53-/-)	Inhibits HDAC1; releases MDM2 and HDAC1 from p53; activates p53	260
		Lymphoid leukemia (MV4-11), myeloid leukemia (Kasumi-1, K562), breast (MCF-7), MV4-11 mice xenografts	Inhibits DNMT1; decreases SP1 protein binding to DNMT1 promoter; decreases global DNA methylation; induces *HIN-1*	261

[1]Abbreviations: AMPK: AMP-activated kinase; APE1: Apurinic/apyrimidinic endonuclease-1; BCL_2: B-cell leukemia/lymphoma 2; BcL-X_L: B-cell leukemia X_L; BTG3: B-cell translocation gene 3; CBP: CREB-binding protein*;* COX-2*:* cyclooxygenase 2; CREBBP: cAMP-responsive element binding protein; CYLD*:* cylindromatosis*;* ER1*:* estrogen receptor 1*;* FOXO3a: forkhead homeobox type O 3a; G6Pase: glucose-6-phosphatase; GSTP1: glutathione S-transferase P 1; HAT: histone acetyltransferase; HIN-1: high in normal-1; hMLH1: human mutL homolog 1; hTERT*:* human telomerase reverse transcriptase; IL-6: interleukin-*6*; MCM: minichromosome maintenance; MDR1*:* multidrug resistant protein 1; MGMT: O^6- methylguanine-DNA methyltransferase; miR: micro RNA; MTA1: Metastasis-associated protein 1; PCAF: P300/CBP-associated factor; Pepck*:* phosphoenolpyruvate carboxykinase; Pgc-1α: peroxisome proliferator-activated receptor γ coactivator 1α; PTEN: phosphatase and tensin homolog; RARβ*:* retinoic acid receptor-β, RECK: reversion-inducing cysteine-rich protein with Kazal motifs; SP1: stimulating protein 1; WIF-1: Wnt inhibitory factor 1

[2]Determined by cell-free biochemical assay

DNMT1 leading to global DNA hypomethylation in lymphoid leukemia cells (192). A recent review describes thoroughly the different epigenetic mechanisms of curcumin in cancer therapy (152).

6.1.1.3. (-)-Epigallo-catechin-3-gallate

EGCG is the major bioactive polyphenol present in green tea. Its antitumor properties have been established including antiangiogenic, antiproliferative, and apoptotic effects (193-194). Moreover, catechins from tea extracts are considered today as potential chemoprevention agents (195). EGCG's anticancer properties may be through epigenetic modulation of both, DNA methylation and histone modifications. As discussed earlier, global DNA hypomethylation and promoter hypermethylation are common in cancer development and lead to genomic instability and gene inactivation, respectively (196), and EGCG prevents both of these processes. For instance, EGCG decreased UVB-induced global DNA hypomethylation in mouse skin carcinogenesis (197). It also reduced promoter methylation of the tumor suppressor genes, *MGMT*, *WIF-1*, *retinoic acid receptor β* (*RARβ*), *p16*, *RECK*, and *hMLH1*, leading to their reactivation in oral, esophageal, colon, prostate, breast, and lung cancer cells (198-203). In breast cancer cells, EGCG also inhibited promoter methylation of *human telomerase reverse transcriptase* (*hTERT*) (204). hTERT is the catalytic subunit of telomerase and expressed in almost 90% of all cancers. Unexpectedly, decreased methylation at *hTERT* promoter by EGCG caused gene inactivation because it enhanced the binding of E2F-1, a tumor suppressor protein and *hTERT* promoter inhibitor. The ability of EGCG to inhibit promoter methylation may be through direct inhibition of DNMT1 (198, 201).

The other epigenetic mechanism reported for EGCG is modulation of histone acetylation by inhibiting HATs and/or inducing HDACs. For instance, EGCG-mediated *hTERT* inhibition is caused by promoting H3Lys9 deacetylation in breast cancer cells (204). EGCG also recruits HDAC3 to *IL-6* promoter and inhibits several HATs, namely, p300/CBP, PCAF, and TIP60, causing histone deacetylation at this promoter and subsequent decrease in *IL-6* expression in kidney, cervical, and myeloid cancer cells (205). In epidermal *in vitro* tumor models, EGCG inhibited Bmi-1, Suz12, and Ezh2

Table 2. Minor plant-derived anticancer drugs as epigenetic modulators

Purified Plant Compound	Plant Origin	Cancer System	Epigenetic Mechanism[1]	References
Polyphenols				
Biochanin A and Daidzein	*Glycine max* (Soybean)	Esophageal/Oral (KYSE 510)	Inhibit DNMT activity; induce *RARβ*	213
Caffeic Acid and Chlorogenic Acid	*Coffea arabica* or *canephora* (Coffee)	Breast (T-47D, MCF-7, MDA-MB-231)	Inhibit DNMT1[2]; decrease *RARβ* promoter methylation	266
Catechin and Epicatechin	*Uncaria rhynchophylla* (Cat's claw herb)	MCF-7, MDA-MB-231	Inhibits DNMT1[2] and DNA methylation	267
Garcinol and derivatives	*Garcinia indica* (Kokam butter tree or Red mango)	Cervical (HeLa)[2]	Inhibits p300	274
			Inhibits p300 and PCAF	276
			Inhibits p300, PCAF and HAT-dependent chromatin transcription	275
Plumbagin	*Plumbago rosea* (Scarlett Leadwort)	Hepatocarcinoma (HepG2), embryonic kidney (HEK 293), Hela[2], mouse liver tissue	Inhibits p300; decreases H3Lys9/14 acetylation; decreases p300-dependent p53 acetylation	277
Pomiferin	*Maclura pomifera* (Osage orange)	HeLa[2]	Inhibits HDAC activity	278
Alkaloids				
Mahanine	*Murraya koenigii* (Curry leaf plant)	Prostate (PC-3)	Inhibits DNMT activity; induces *RASSF1A*	279
Sanguinarine	*Sanguinaria canadendid* (Bloodroot)	HeLa, mouse liver tissue	Inhibits p300 and PCAF[2]; decreases H3Lys4/9 acetylation and H3Arg17/Lys4 methylation	288
Organosulfur compounds				
Allyl mercaptan	*Allium* vegetables (Onion/Garlic)	HT29, HeLa[2]	Inhibits HDAC activity; increases H3 acetylation of *p21* promoter; induces *p21*	295
Diallyl disulfide		Colon (Caco-2, HT-29), HeLa[2]	Inhibits HDAC activity; increases H3Lys9/14 and H4Lys 12/16 acetylation; induces *p21*	294
S -Allyl-mercapto cysteine		Colon (Caco-2), breast (T-47D), myeloid leukemia (DS19)	Inhibits HDAC and HAT activities; increases H2A, H2B, H3 and H4 acetylation; decreases histone phosphorylation	293
Terpenoids				
Lycopene	*Solanum lycopersicum* (Tomato)	Breast (MDA-MB-468, MCF10A)	Decreases *GSTP1, RARβ2* and *HIN-1* promoter methylation; induces *GSTP1*	215
Triptolide	*Tripterygium wilfordii* (Three-wing-nut Chinese herb)	Myeloid Leukemia (RPMI8226)	Inhibits HMT; decreases H3Lys9 and H3Lys27 methylation	300
			Inhibits HDAC8; increases H3 and H4 acetlyation	301
		Sarcoma (HT-1080)	Increases *MMP-9* promoter methylation; inhibits *MMP-9*	302
Thymoquinone	*Nigella sativa* (Black seed)	Lymphoma (Jurkat)	Inhibits UHRF1/DNMT1/HDAC1 complex	303

[1]Abbreviations: GSTP1: glutathione S-transferase P 1; HIN-1: high in normal-1; MMP9: matrix metallopeptidase 9; RARβ: retinoic acid receptor-β; RASSF1A: ras-association domain family 1 A [2]Determined by cell-free biochemical assay

polycomb proteins and decreased H3Lys27 trimethylation (206). Furthermore, EGCG decreased the expression of cell cycle activators, while it increased epidermal differentiation markers (206). Recently, EGCG was shown to induce *miRNA-16* leading to inhibition of its target gene, *Bcl-2*, in liver cancer cells (207).

6.1.1.4. Genistein

Genistein (4',5,7-trihydroxyisoflavone), the most abundant isoflavone found in soybean, is a chemopreventive agent against many cancers (208). Genistein exhibits estrogen agonist and antagonist effects and inhibits protein tyrosine kinases, oxidative stress, and angiogenesis (209). Similar to EGCG, genistein decreases promoter methylation of tumor suppressor genes leading to their reactivation in cancers. For instance, genistein reactivated *BTG3*, *MGMT*, *RARβ*, *p16*, *p57*, and *glutathione S-transferase P1* (*GSTP1)* by promoter hypomethylation in oral, esophageal, prostate, breast, kidney, and myeloid cancer cells (210-215). The ability of genistein to inhibit promoter methylation may be through inhibition of general DNMT activity, specific inhibition of DNMT1, DNMT3a, and/or DNMT3b activities, or inhibition of methyl-binding domain protein 2 activity (209-211, 213). Genistein, like EGCG, decreased *hTERT* promoter methylation causing E2F-1-dependent *hTERT* inactivation (209). This inhibition was enhanced by genistein-induced increases in trimethyl-H3Lys9 and decreases in dimethyl-H3Lys4 on *hTERT* promoter (209).

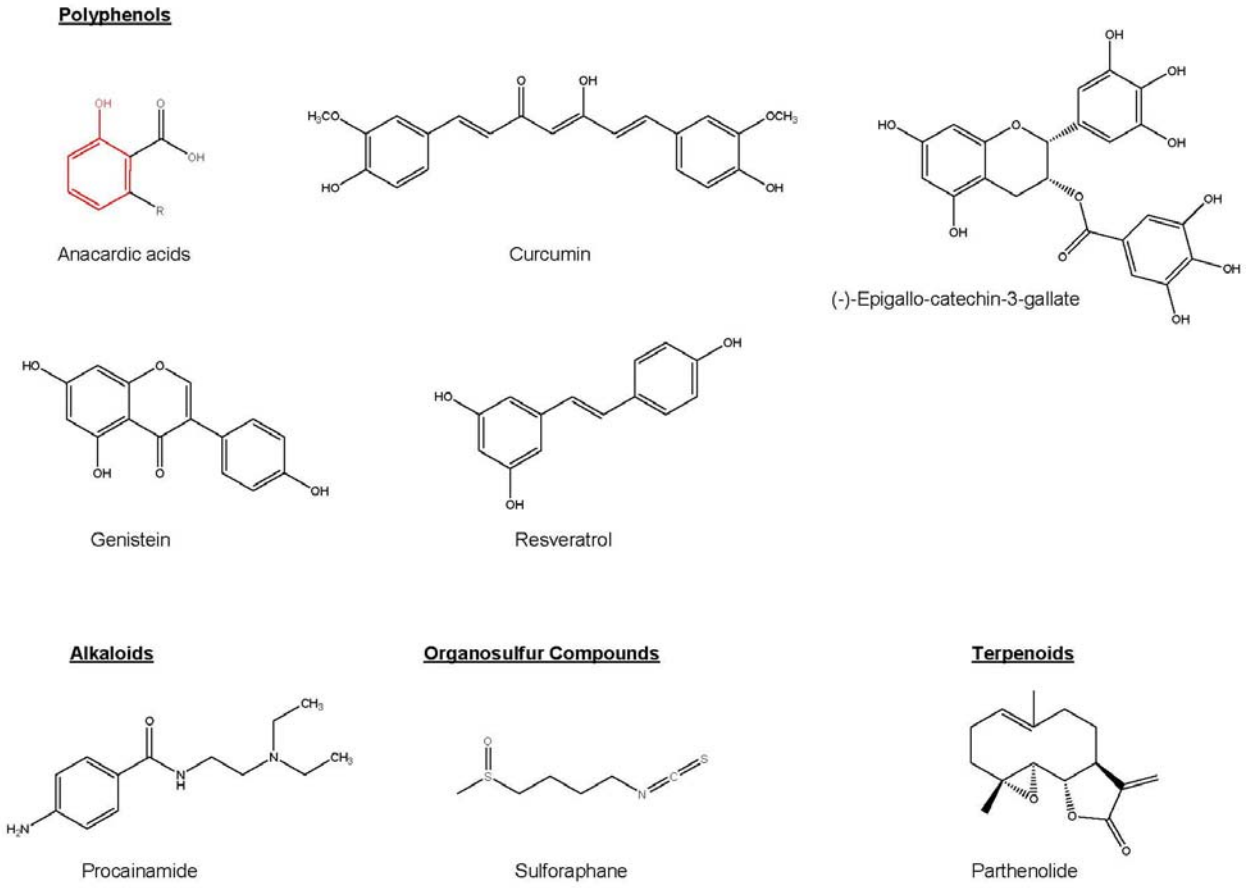

Figure 1. Structures of major plant-derived anticancer drugs that work through epigenetic mechanisms

Unlike EGCG, genistein only causes histone acetylation by inhibiting HDACs and/or activating HATs. In prostate and kidney tumor cells, genistein inhibited SIRT1 and induced p300, PCAF, CREBBP, and HAT1 (210-211, 216-217). This lead to acetylation of H3Lys9 at *PTEN*, *CYLD*, *p53*, and *FOXO3a* promoters (216), to acetylation of H3, H4, and H3Lys4 at *p16* and *p21* promoters (217), and to acetylation of H3, H4, di-methyl H3Lys4, and tri-methyl H3Lys4 at *BTG3* promoter (210-211). These acetylation patterns caused activation of all the respective genes (210-211, 216-217). Genistein also inhibited HDAC6 leading to acetylation and inactivation of Hsp90 chaperone that is normally required to stabilize the AR, a transcription factor essential for tumor progression in prostate cancer cells (218). Notably, one report showed decreased H3 acetylation by genistein. Genistein decreased H3 acetylation in breast cancer cells and inhibited the increase of acetylated H3 caused by HDAC inhibitors (219).

A new role of genistein in miRNA regulation has recently emerged. In uveal melanoma, genistein repressed miRNA-27a and its target gene, *ZBTB10* (220). In prostate cancer cells, genistein abrogated all members of the minichromosome maintenance (MCM) gene family, which is normally essential for DNA replication and frequently upregulated in many cancers (221). In fact, genistein inhibited *MCM2* by inducing the upstream miRNA-1296 (220). In ovarian cancer cells, genistein induced 53 miRNAs and upregulated ERα and ERβ leading to reduced invasion and migration (222).

6.1.1.5. Resveratrol

Resveratrol is abundant in red grapes and nuts where it acts as a phytoalexin (223). Resveratrol's health benefits are diverse and include cardio- and neuro-protection and cancer prevention (223-225). Resveratrol is a well-established inducer of SIRT1 in breast, lung, kidney, and skin cancers *in vitro* and *in vivo* (226-231) and it decreases tumorigenesis in murine skin tumors in a SIRT1-partially dependent manner (229). Resveratrol can also inhibit HAT activity, in particular p300 (228, 230, 232). Resveratrol's effect on SIRT1 and HAT activities reduced H3Lys9, H3Lys14, and H4 acetylation (226, 230, 233) and was associated with decreased expression of the oncogenes, *survivin* (226), *COX-2* (233), *MDR1,* and *Bcl-*x_L (228). Resveratrol also decreased p300-induced acetylation of Apurinic/apyrimidinic endonuclease-1 (APE1) and RelA/p65 (228, 230, 232). APE1 is an essential enzyme for base excision repair, and resveratrol-mediated deacetylation induced its activity in kidney and cervical cancer cells (232). In contrast, deacetylation of NF-kB by resveratrol treatment reduced its transcriptional activity in several cancer types (228, 230). Elevated NF-κB signaling

in cancer cells correlates with chemo-and radio- resistance, so its targeted inhibition by resveratrol may be crucial to resensitize cancer cells to chemotherapy (234). Finally, resveratrol was recently shown to inhibit Metastasis-associated protein 1 (MTA1) and to destabilize the MTA1/HDAC1/p53 complex leading to increased p53 acetylation and activation and, hence, increased expression of p53 target genes, *p21* and *bax* (235). MTA1 is a part of the nucleosome remodeling deacetylation (NuRD) corepressor complex needed for post-translational modifications of histones and nonhistone proteins leading to transcriptional inactivation. MTA1 overexpression signifies tumor aggressiveness in prostate cancer, so its targeted inhibition by resveratrol is promising for late-stage tumors.

6.1.2. Alkaloids: procainamide and derivatives

Alkaloids are naturally occurring compounds containing basic nitrogen atoms although some neutral (236) and weakly acidic members exist (237) (Figure 1). There is no clear boundary between alkaloids and other nitrogen-containing molecules (238); compounds like amino and nucleic acids are not considered alkaloids (236). Recent alkaloid classifications are based on the carbon skeleton or biogenetic precursor. Alkaloids include well-known antitumor drugs, such as the mitotic inhibitors, vinblastine, vincristine, and colchicine (239). Procainamide, an alkaloid extracted from the Coca plant, is a non-nucleoside drug approved by the U. S. Food and Drug Administration (FDA) for the treatment of cardiac arrhythmias (240). Procainamide also shows promising anticancer properties particularly through epigenetic modulation of DNA methylation. It inhibits DNMT activity in myeloid leukemia cells (241) and specifically DNMT1 in colon cancer cells (240). DNMT1's affinity to its two substrates, hemimethylated DNA and SAM, was decreased by procainamide through partial competitive inhibition. Procainamide is not a potent inhibitor of DNMTs 3a and 3b and could decrease methylated cytosines in parental or *DNMT3b* -/- colorectal cancer cells but not in *DNMT1*-/- counterparts (240). The inhibition of DNMT activity by procainamide leads to decreased promoter methylation of several genes, thus, inducing their expression. For instance, procainamide reversed *GSTP1* CpG island hypermethylation and restored its expression in prostate cancer *in vitro* and in xenograft mouse models (242). Procainamide similarly decreased methylation of *estrogen receptor* (*ER*)*, RARβ* and *p16* promoter regions, effectively inducing all of these genes in bladder and breast cancer cells and in a breast cancer mouse xenograft model (243). Procainamide also decreased *WIF-1* promoter methylation leading to *WIF-1* induction in lung cancer cells (244). Procaine, an anesthetic drug related to procainamide, was shown to directly bind to GC-rich DNA and to decrease global DNA methylation and *RARβ2* promoter hypermethylation, thus, re-expressing this tumor suppressor gene in breast cancer cells (245). Similarly, procainamide reversed cadmium-induced genomic hypermethylation in cadmium-transformed prostate cancer cells (246).

6.1.3. Organosulfur compounds: sulforaphane

Organosulfur compounds are organic compounds that contain sulfur (Figure 1) and are classified according to their sulfur-containing functional groups (thioethers, thioesters, thioacetals; thiols, disulfides, polysulfides; C-S double and triple bonds; sulfonic acids, esters, amides; sulfuranes, persulfuranes) (247). Organosulfur compounds have been widely used in preventing platelet aggregation and in cancer therapy (248). The organosulfur compound sulforaphane is a derivative of glucoraphanin found in cruciferous vegetables such as broccoli. Sulforaphane has diverse biological effects including cell cycle arrest, apoptosis, and heme oxygenase and Phase 2 detoxifying enzyme induction, such as NAD(P)H:quinone reductase (NQO1) (249). Upregulation of Phase 2 metabolism by sulforaphane helps remove body genotoxins leading to cancer prevention at the initiation phase (249).

Another way sulforaphane mediates its anticancer effects is through epigenetic mechanisms, and, in fact, it is a well-established HDAC inhibitor (249). Sulforaphane decreases HDAC activity causing an increase in total and promoter-specific H3 and H4 acetylation in kidney, colon, and prostate cancer cells and in colon and prostate cancer mouse models (250-253). For instance, sulforaphane increases H3 and/or H4 acetylation at the *p21* and *bax* promoters, hence, inducing these genes in these cancers (250-253). In human subjects, HDAC activity in peripheral blood mononuclear cells was inhibited as early as 3 h after a single consumption of Broccoli (253). Recently, sulforaphane was found to specifically inhibit HDAC6 in prostate cancer cells causing acetylation and subsequent degradation of an AR chaperone, Hsp90 (254). In the absence of Hsp90, the expression of its target gene, *E-twenty six related gene* (*ERG*), is inhibited (254). ERG is a transcription factor overexpressed in human prostate cancer (255) leading to enhanced invasiveness and growth (256). Thus, therapies, like sulforaphane, which reduce AR and ERG proteins, are promising for prostate cancer prevention and treatment.

6.1.4. Terpenoids: parthenolide

Terpenes are hydrocarbons derived from five-carbon isoprene units (Figure 1); they can be modified to terpenoids through addition of oxygen atoms or skeletal rearrangements. Many terpenes have promising potential against inflammation and cancer and are currently in cancer clinical trials (24). Parthenolide, a 15-carbon terpenoid (sesquiterpene lactone), is commonly extracted from the European feverfew herb (*Tanacetum parthenium*), which is traditionally used for the treatment of arthritis, headaches, fevers, and local skin irritations. Parthenolide is currently among the most promising anticancer drugs in clinical development and the only small molecule, to date, that selectively targets cancer stem cells while sparing normal ones (257). Parthenolide may be also considered the first example of a small molecule that specifically depletes HDAC1 proteins without affecting other class I/II HDACs in breast, brain, connective tissue, and colon cancer cells (258-260). HDAC1 depletion did not occur through the IκB kinase 2 (IKK2), a known parthenolide target and regulator of HDAC1, or through the canonical NF-κB and JNK pathways usually targeted by parthenolide (258). Although parthenolide is not a classic HDAC inhibitor, it targets HDAC1 to proteasomal-mediated degradation

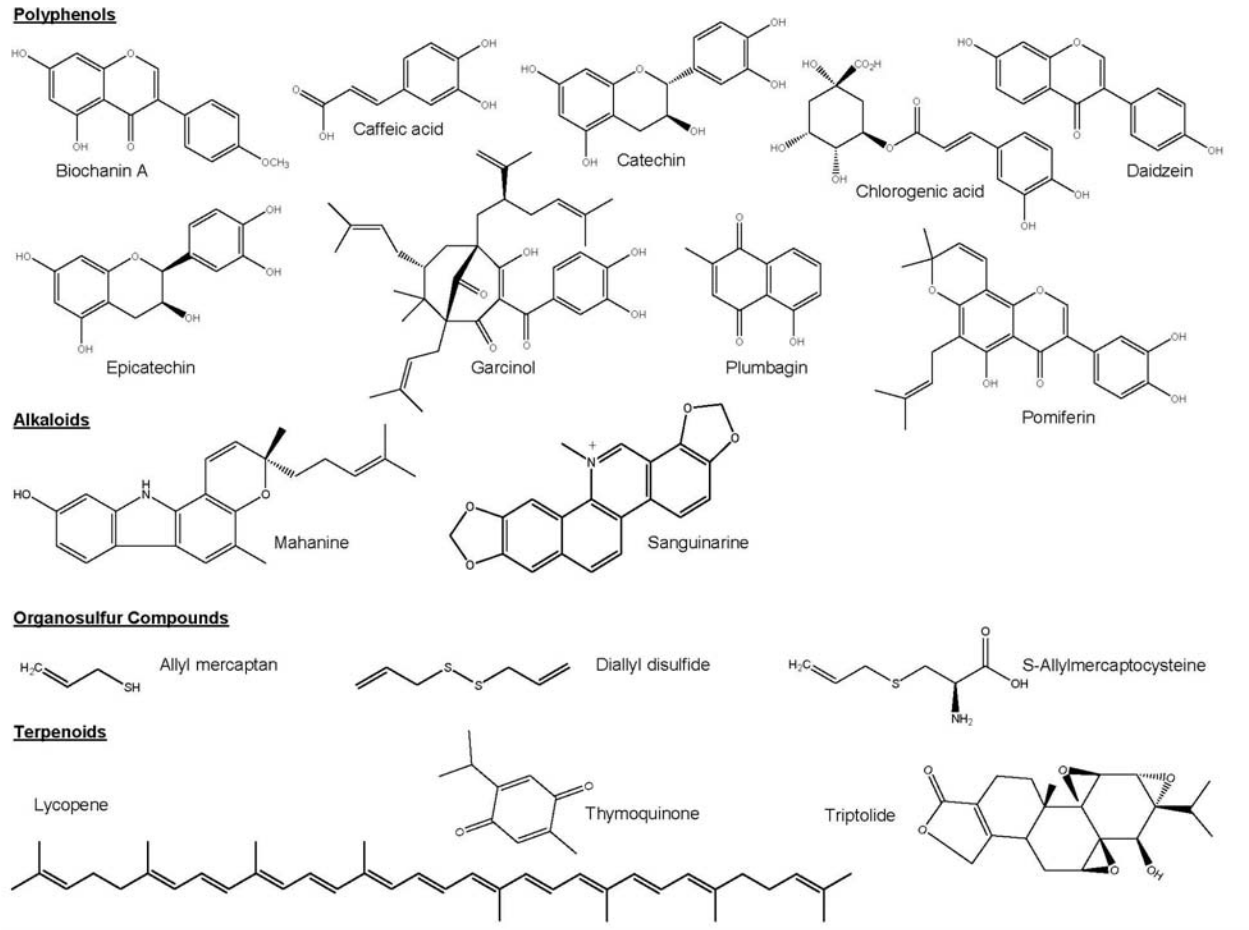

Figure 2. Structures of minor plant-derived anticancer drugs that work through epigenetic mechanisms

causing H3 acetylation on the *p21* promoter and subsequent *p21* transcription, which are typical effects of HDAC inhibitors (258). Moreover, parthenolide released p53 from MDM2 and HDAC1, hence, causing p53 reactivation (260). We have recently shown that parthenolide also inhibits HDAC1 in skin and colon cancer cells (Ghantous *et al.* unpublished data) suggesting a HDAC1 inhibitory mechanism in several cancers.

Parthenolide also inhibits DNMT1 in lymphoid and myeloid leukemias, *in vitro* and *in vivo* (261). Parthenolide's γ-methylene lactone group alkylates the proximal thiolate of Cys^{1226} of DNMT1 catalytic domain leading to inhibition of DNMT activity (261). Parthenolide also down-regulates DNMT1 expression by interfering with the binding of the transcription factor Sp1 to the *DNMT1* promoter (261). These dual functions of parthenolide result in the observed decrease, both *in vitro* and *in vivo,* of global DNA methylation. For instance, parthenolide reactivated the tumor suppressor *HIN-1* gene *in vitro* by decreasing its promoter methylation (261). Some DNA methylation inhibitors derived from plants, such as parthenolide, procainamide, and EGCG that abrogate specific DNMTs lead to reduced toxicity relative to the nucleoside analogues that trap chunks of DNMTs (51). The discovery of such novel hypomethylating agents is essential to broaden the spectrum of anticancer drugs that work through epigenetic therapy.

6.2. Minor plant-derived anticancer drugs as epigenetic modulators

Other plant-derived anticancer drugs have shown promise as epigenetic modulators but were classified as minor compounds (Table 2), as their epigenetic mechanisms are less established than the previously described major ones (Table 1). Similarly to the natural anticancer drugs covered previously (Table 1), most of these drugs also belong to the polyphenol group of plant secondary metabolites, whereas others are part of the alkaloid, terpenoid, and organosulphur groups (Figure 2).

6.2.1. Polyphenols

Isoflavones, a class of polyphenols, are known to possess anticancer properties in a variety of cancers such as prostate, stomach and lung (262-265). The soy isoflavones, biochanin A, and daidzein are anticancer drugs that have been shown to inhibit DNMT activity and induce *RARβ* expression in esophageal cancer cells. (199). However, they are weaker than genistein in inhibiting DNMT activity and in reactivating *RAR*β in esophageal cancer cells. This

reinforces the correlation between DNMT activity and the reactivation of methylation silenced genes by these dietary isoflavones (199).

Catechol-containing polyphenols, such as caffeic and chlorogenic acid, catechin and epicatechin, also modulate DNA methylation. They are potent non-competitive inhibitors of the prokaryotic M.SssI DNMT and the human DNMT1 and cause a concentration-dependent inhibition of DNA methylation in the *RARβ* promoter in human breast cancer cells, without significantly affecting global DNA methylation (266-267). Catechol-containing dietary polyphenols are substrates of catechol-O-methyltransferase (COMT), an enzyme which catalyzes the *O* - methylation of these substrates (268-270). Kinetic studies have shown that this reaction is responsible for increasing the levels of S-adenosyl-L-homocysteine (SAH). Since SAH is a powerful inhibitor of DNA methylation (266, 271-273) it is suggested that caffeic and chlorogenic acids, along with tea catechins, may abrogate DNA methylation through the increased formation of SAH. (266-267).

Alternatively, polyphenols can also act as epigenetic modulators of tumorigenesis by targeting histone modifications. For instance, the polyphenols garcinol and its derivatives, isogarcinol and LTK-14, which are isolated from the fruit rind of Red mango (*Garcinia indica),* inhibit p300 in cervical cancer cells (274), making garcinol the first cell permeable HAT inhibitor to be reported (275). Unlike the nonspecific HAT inhibitors garcinol and isogarcinol, LTK-14 is a specific p300 HAT inhibitor and can also act as a noncompetitive inhibitor for both core histone and acetyl-CoA binding sites (274). Furthermore, garcinol inhibits PCAF (276) and HAT-dependent chromatin transcription, without affecting DNA template transcription and induces chromatin fragmentation, hence, apoptosis in cervical cancer cells (275). The mechanisms of action of natural HAT inhibitors, such as garcinol, are poorly understood. Interestingly, using genome-wide analysis (2261 genes), more than 70% of those genes were down- regulated in garcinol-treated cervical cancer cells, and several of them were found to be proto-oncogenes (275), implying that garcinol's anticancer activities may be due to the downregulation of these genes by inhibiting their acetylation. Similarly, plumgabin, a hydroxynapthoquinone isolated from the roots of the Scarlett leadwort *(Plumbago rosea)*, decreases H3Lys9/14 acetylation and total histone acetylation in hepatocarcinoma cells and mouse liver tissue, respectively (277). Interestingly, plumgabin was found to inhibit the acetylation of p53 specifically at the p300 substrate, lysine 373, and not the PCAF substrate, lysine 320, in immortalized kidney cells. Furthermore, plumbagin is a non-competitive inhibitor of p300 HAT activity in cervical cancer cells. Docking studies revealed that the single hydroxyl group on the carbon 5 (C5) was found to be essential for this p300 HAT inhibition (277). On the other hand, pomiferin, a polyphenol extracted from the fruits of Osage orange (*Maclura pomifera*), inhibits HDAC activity in cervical cancer cells and reduces the growth of prostate and colon cancer cells (278).

6.2.2. Alkaloids

Mahanine, an alkaloid purified from the curry leaf plant (*Murraya koenigii*), inhibits total DNMT activity, hence reactivating the epigenetically silenced tumor suppressor gene, *RASSF1A* (279). *RASSF1A* hypermethylation occurs in at least 37 tumor types (279), including 80% of examined small cell lung cancers (280-281), over 60% of breast cancers (280-281), and over 70% of prostate cancers (282-283). Furthermore, it was shown that mahanine's reactivation of *RASSFA1* arrested the cell cycle by specifically decreasing cyclin D_1 expression and not cyclins A_1, B_1 or E_1, in prostate cancer cells (279). Recently, a fluorescent carbazole analogue of mahanine, in addition to inducing RASSF1A and cyclin D_1 expression, was found to increase the shuttling of DNMT3b and not DNMT3a from the nucleus to the cytoplasm of prostate cancer cells treated with this analogue (284).

Sanguinarine, an alkaloid isolated from the roots of poppy fumaria species such as *Sanguinaria canadendid* or bloodroot, possesses anti-microbial, anti-inflammatory, anti-oxidant, and proapoptotic activities (285-287). Sanguinarine is a highly cell permeable compound (288) and a potent inhibitor of cell growth and NF-κB activity (289). Unlike mahanine, sanguinarine modulates histone modifications but not DNA methylation. Sanguinarine diffuses through cell membranes and strongly intercalates within DNA, associates with chromatin and core histones, and consequently alters chromatin structure (288). In cervical cancer cells, sanguinarine decreases epigenetic marks associated with transcriptional activation (288). In particular, it decreases H3Lys4/9 acetylation, by inhibiting p300 and PCAF activities, and reduces H3Arg17/Lys4 methylation, by inhibiting the lysine and arginine methyltransferases, G9a and PRMT4/CARM1, respectively (288). In addition to sanguinarine being a potent inhibitor of HAT activity *in vitro,* it can also cause a drastic reduction of histone acetylation in mice liver treated with sanguinarine (288). Sanguinarine modulates global gene expression in cervical cancer cells; upregulating genes involved in apoptosis, such as *bax* and the IAP antagonist *DIABLO,* and downregulating genes such as the activating transcription factor *ATF6* (288).

6.2.3. Organosulphur compounds

Many plant-derived organosulphur compounds, such as the allyl sulphur derivatives commonly found in garlic, possess anticancer properties in a variety of cancer cells (290-292). Several of these compounds act as epigenetic modulators in cancer cells by targeting histone modifications. Interestingly, S-Allylmercaptocysteine (SAMC), isolated from *Allium* vegetables such as garlic, exhibits its growth inhibitory properties by suppressing both HDAC and HAT activities and increasing H2A, H2B, H3 and H4 acetylation in myeloid leukemia, colon, and breast cancer cells (293). Surprisingly, treatment with SAMC did not reveal a change in the ratio of enzyme activities that would favor an increase in histone acetylation levels. Additionally, SAMC was found to decrease H1 and H3 phosphorylation, which may be responsible for SAMC's apoptotic activity in erythroleukemic cells (293). Other garlic compounds, such as diallyl sulfide and allyl

mercaptan, both inhibit histone deacetylation by reducing HDAC activity in cervical and colon cancer cells (294-295). Diallyl sulfide and allyl mercaptan also increase H3Lys9/14 acetylation, inducing p21 expression in colon and cervical cancer cells (294-295). However, diallyl sulfide induced the hyperacetylation of H4Lys12/16 in only colon cancer cells. Moreover, allyl mercaptan acts as a competitive HDAC inhibitor in cervical cancer cells, and concurrent with the H3 hyperacetylation, it was found to enhance the binding of Sp3 and p53 to the *p21* promoter region, inducing p21 in colon cancer cells (295).

6.2.4. Terpenoids

Several terpenoids were shown to modulate DNA methylation of cancer cells. Lycopene, a potent antioxidant carotenoid found in tomatoes and other red fruits, exhibits anticancer properties in a variety of cancers (296-298) and induces the tumor suppressor genes RARα and connexin 43 in breast cancer cells (299). As an epigenetic modulator, lycopene, at dietary relevant low doses, causes the demethylation of the tumor suppressor gene promoter *GSTP1*, thus inducing its expression in breast cancer cells, and partially demethylates the promoters of *RARβ2* and *HIN-1* tumor suppressors in breast cancer cells, but without inducing their expression (215).

Some plant-derived drugs mediate their anticancer activities by modulating various epigenetic mechanisms simultaneously. For instance, the terpenoids triptolide, extracted from *Tripterygium wilfordi,* commonly known as the three-wing-nut, and thymoquinone, extracted from *Nigella sativa* or the black seed, modulate chromatin modifications by inhibiting polycomb group proteins. Triptolide inhibits the histone methyltransferases SUV39H1 and EZH2, which also is the catalytic subunit of the polycomb repressive complex 2 (PRC2), by reducing the level of their transcripts (300). It is thought that triptolide's inhibition of these HMTs causes the decreased H3Lys9 and H3Lys27 global trimethylation in multiple myeloma cells, since SUV39H1 and EZH2 particularly trimethylate H3Lys9 and H3Lys27, respectively (300). Recently, triptolide was found to decrease H3 and H4 acetylation by decreasing the mRNA and protein expression of HDAC8 in multiple myeloma cells (301). On the other hand, triptolide increases *MMP-9* promoter methylation in sarcoma cells, silencing its expression (302). Recently, thymoquinone induced apoptosis in lymphoma cells, *via* a caspase-dependent mechanism (303) and this was associated with upregulated p73, a cell cycle checkpoint regulator. Consequently, thymoquinone downregulated the epigenetic integrator UHRF1, and its partners DNMT1 and HDAC1 in the latter cells (303).

7. PLANT EXTRACTS WITH ANTICANCER AND EPIGENETIC ACTIVITES

Recently, there has been an increased interest in investigating the anticancer and epigenetic activities of crude plant extracts containing adjuvant substances which may enhance the activity of the components that are responsible for this effect (304). We will next review crude plant extracts, most of which are polyphenol rich, as plant-derived drugs with promising anticancer and epigenetic properties (Table 3). Table 3 indicates whether the epigenetic mechanisms of these extracts are based on cancer cell lines and/or *in vivo* animal models. In particular, green tea extracts and black tea polyphenols are in cancer clinical trials (154).

7.1. Polyphenol-rich plant extracts

Polyphenols possess potent anti-oxidant and anticancer properties (161, 305). Recently, polyphenol rich plant extracts have shown epigenetic activities in a variety of cancer types by modulating promoter methylation of critical tumor genes. The Italian Annurca apple flesh is rich in several potent polyphenols such as caffeic and chlorogenic acid, catechin, and epicatechin. This polyphenol rich extract was shown to inhibit DNMT1 and DNMT3b in colon cancer cells, decreasing *hMLH1, p14*, and *p16* promoter methylation, hence reactivating these tumor suppressor genes (306).

Green tea rich polyphenol extract was found to decrease *CDX2* and *p16* promoter methylation in colon and gastric cancer cells, as well as in primary gastric carcinoma cells (307-308). Moreover, green tea intake was also associated with decreased promoter methylation of genes that are commonly hypermethylated and lost in gastric cancers, including the bone morphogenetic protein 2 (*BMP-2*), calcium channel related (*CACNA2D3*), the transcription factor *GATA-5,* and the *ER* in primary gastric carcinoma cells (308). Furthermore, green tea polyphenols were recently found in Azoxymethane-treated $Apc^{Min/+}$ mouse model of intestinal cancer (309), to induce retinoid X receptor *RXRα* by decreasing promoter methylation, in addition to inhibiting β-catenin and its downstream target cyclin D_1.

Black tea polyphenol extracts were recently shown to modulate histone acetylation by inhibiting the expression of HDAC1 in a dimethylaminoazobenzene (DAB)-induced rat hepatocarcinogenesis model, in addition to modulating markers of invasion and angiogenesis, reducing the incidence of DAB-induced hepatomas (310).

7.2. Crude plant extracts

The Japanese rose (*Rosa rugosa*), allspice (*Pimenta dioica*) and pineapple guava (*Feijoa sellowiana*) crude extracts were shown to modulate histone acetylation in prostate cancer cells. *Rosa rugosa* is a species of rose native to East Asia, and has been used as a folk ailment for the treatment of various disorders such as chronic inflammatory diseases and diabetes as well as exhibiting anticancer properties (311-313). Recently, *Rosa rugosa* methanol extracts and allspice water extracts, (from the dried berry of *Pimenta dioica*), were shown to be potent HAT inhibitors, in particular, p300 and CBP (314-315). Furthermore, both plant extracts induced AR, H3 and H4 hypoacetylation in the promoters of the target genes *PSA* and *B2M*, and caused a decrease in AR-mediated transcription of AR-regulated genes such as *NKX-3.1* by *Rosa rugosa* methanol extracts and of *TSC22* by *Pimenta dioica* water extracts in prostate cancer cells (314-315).

Table 3. Plant extracts with anticancer and epigenetic activities

Plant Extract	Cancer System	Epigenetic Mechanism	References
Polyphenol-Rich Extracts			
Annurca Apple Extract	Colon (RKO, SW48, SW480)	Inhibits DNMT1 and DNMT3b; decreases *hMLH1, p14* and *p16* promoter methylation; induces these genes	306
Green Tea Extract	Colon (RKO), Gastric (GT3TKB, MKN74)	Decreases *CDX2* promoter methylation	307
	Primary gastric carcinoma cells	Decreases *CDX2, BMP-2, p16, CACNA2D3, GATA-5*, and *ER* promoter methylation; inducing their expression	308
	Azoxymethane-treated $Apc^{Min/+}$mouse model of intestinal cancer	Decreases *RXRα* promoter methylation, inducing *RXRα* expression	309
Black Tea Polyphenols	DAB-induced rat hepatocarcinogenesis model	Inhibit HDAC1 expression	310
Crude Plant Extracts			
Rosa rugosa (Thunb/ Japanese rose) and *Pimenta dioica* (Allspice)	Prostate (LNCaP)	Inhibit p300 and CBP activities; decrease H3 and H4 acetylation; inhibit AR, H3 and H4 acetylation in the *PSA* and *B2M* promoters; inhibit AR-regulated genes *PSA, NKX-3.1* and *TSC22* (allspice)	314-315
Feijoa sellowiana (Pineapple guava)	Myeloid Leukemia (NB4), Prostate (LNCaP)	Increases H3 acetylation; inhibits HDAC1 activity	321

Abbreviations: B2M: β-2-microglobulin; BMP-2: bone morphogenetic protein 2; CACNA2D3: calcium channel related; DAB: Dimethylaminoazobenzene; ER: estrogen receptor; GATA-5: transcription factor; hMLH1: human mut-L homolog 1; NKX-3.1: a homeobox gene; PSA: prostate specific antigen; TSC22: transforming growth factor-simulated clone-22

Crude extracts of *Feijoa sellowiana*, or pineapple guava, also have the ability to modulate histone acetylation. *Feijoa sellowiana*, originally native to South America yet widely grown in the Mediterranean region, is an evergreen shrub that was shown to possess anticancer (316) (317) and anti-microbial activities (318-320). Pineapple guava extracts display cancer-cell selectivity and were shown to induce apoptosis in leukemia and prostate cancer cells by inducing the CDKIs p16 and p21, as well as increasing H3 acetylation (321). Its purified active component, a flavones compound, inhibited HDAC1 activity and induced apoptosis in leukemic cells (321).

8. EPI-DRUGS: STRUCTURE-ACTIVITY RELATIONSHIP

Structure-activity relationship (SAR) studies for epi-drugs were mostly performed on DNA methylation and histone deacetylation inhibitors. SAR analyses of plant-derived compounds with respect to their anticancer properties are numerous but not considerably relevant to epigenetic effectors, probably due to the newly discovered potential of plant-derived compounds in epigenetics. Another reason is that the way plant-derived compounds modulate epigenetic targets is not always through chemical inhibition or direct effects but rather by altering cell-signaling pathways that eventually lead to epigenetic regulation. This section highlights the major functional groups required for activity of DNA methylation and HDAC inhibitors, pinpointing, where possible, to examples from plant-derived compounds.

8.1. DNA methylation inhibitors

DNA methylation inhibitors can be divided into two groups: nucleoside and non-nucleoside analogues (6). Nucleoside analogues, such as 5-azacytidine and zebularine, have a modified cytosine linked to either a ribose or a deoxyribose unit. These analogues can be incorporated into DNA during cell division. If in ribonucleoside form, these analogues are first integrated into RNA and subsequently reduced by ribonucleotide reductase into a deoxy form which can be then incorporated into DNA. During DNA replication, DNMTs flip out cytosines from DNA and transfer a methyl group to C5 of the base before being released. In the case of DNA-incorporated nucleoside analogues, a modification at C5 of cytosine covalently binds the enzyme preventing its release. Non-nucleoside analogues, on the other hand, decrease DNA methylation by direct binding to the catalytic regions of DNMTs (6) or through indirect mechanisms which, in both cases, do not require incorporation into DNA. Parthenolide, for example, inhibits DNMT1 through alkylation of the thiolate of the catalytic cysteine (Cys^{1226}) by its α-methylene-γ-lactone (322). Similarly, curcumin alkylates the catalytic cysteine of DNMT1 (192). EGCG binds directly to DNMT1 through hydrogen bonding (267). Caffeic acid and chlorogenic acid inhibit DNMT1 because, similar to other catechols, they undergo O-methylation to yield methylated catechols and SAH, a feedback inhibitor of DNMTs (323). Procainamide inhibits DNA methylation by binding to CG-rich DNA (324). Plant-derived epi-drugs may not be as robust inhibitors as nucleoside analogues but might work better in some contexts than others (6).

8.2. Histone deacetylase inhibitors

Seven major classes of classical HDAC inhibitors exist: hydroxamic acids, short chain fatty acids, aminobenzamides, cyclic tetrapeptides, hybrid cyclic tetrapeptides, cyclic peptide-derived small molecule inhibitors, and electrophilic ketones (21, 80, 97). All classes harbor three structural motifs: (1) a ZBG which interacts with the zinc ion at the bottom of the active site in HDACs, (2) a capping group which binds to amino acids at the active site entrance and at the protein surface, and (3) a

linker domain which ensures proper positioning of the former two motifs (97). In hydroxamic acids, the hydroxamate group acts as the ZBG (21). Short chain fatty acids often bind to the catalytic centers of HDACs. Aminobenzamides, such as MS-275, may interact with the zinc ion in the HDAC active site in a manner similar to hydroxymates or may bind at an allosteric site (21). It is still unclear which of these two modes occurs or whether both do. Cyclic tetrapeptides typically contain a hydrophobic capping group and a long aliphatic amino acid (often *L*-Aoe or *L*-Aoda) (97) that can bear an epoxyketone, which covalently binds an active site nucleophile in HDACs (21) or acts as a ZBG (97). Hybrid cyclic tetrapeptides have been synthesized by adding to a cyclic tetrapeptide another ZBG, namely a hydroxamic acid or a thiol group (97). Also, cyclic peptide-derived small molecule inhibitors have been synthesized from the cyclic tetrapeptide, Apcidin (325). These are acyclic derivatives bearing the crucial *L*-Aoda chain (97). Electrophilic ketones, in aqueous solutions, equilibrate with their corresponding hydrates, which chelate zinc in the HDAC active center. Electrophilic ketones were developed in an attempt to shift away from hydroxamic ZBGs which often associate with poor pharmacokinetic profiles (97). Although parthenolide has been shown to inhibit HDAC1 by proteasomal-mediated degradation (326), its epoxy and/or electrophilic ketone (α-methylene-γ-lactone) might be able to attack nucleophilic sites in the HDAC1 active center, in a manner similar to its inhibition of DNMT1. S-allylmercaptocysteine and sulforaphane-cysteine, the metabolites of DADS and sulforaphane, respectively, have a linker domain and a carboxylic functional group which may enable them to inhibit HDACs in a manner similar to the short chain fatty acid butyrate (327). In sulforaphane-cysteine, the α-amino group can H-bond with histidine residues in the HDAC enzyme pocket, and the carboxylic group can form a bidentate ligand with the zinc ion in the active site (327). Molecular docking with HDAC8 showed that chlorogenic acid or curcumin do not interact with the zinc ion but form two H-bonds with amino acid residues at the entrance of the active site cavity (328). Caffeic acid interacts with the zinc ion and forms one H-bond at the active site (328).

9. STRATEGIES FOR COMBINING EPIGENETIC MODIFIERS IN CANCER THERAPY

Epigenetic therapy can be designed in different strategies depending on whether the epigenetic modulators are used as single agents or in sequential treatment with other drugs (48). For instance, pretreatment with DNMT or HDAC inhibitors can restore the expression of tumor suppressor genes and sensitize tumor cells to chemotherapeutic agents. Pretreatment of solid tumors *in vitro* with the 2'-deoxycytidine (DAC), a nucleoside analogue, sensitizes tumor cells to cisplatin treatment (329). Also concomitant treatment with 5 azacytidine, another nucleoside analogue, and doxorubicin induces synergistic cytotoxicity in multiple myeloma cells (330). Sequential treatment of leukemia cells with DAC followed by cytarabine induces synergistic cytotoxicity. Surprisingly, cytarabine inhibits DAC induced global hypomethylation in leukemia cells, probably due to the selective killing of hypomethylated cells by cytarabine (331). Conversely, sequential treatment with chemotherapy to debulk the tumor followed by DNMT or HDAC inhibitors to restore the differentiation program of chemotherapy resistant tumor-initiating cells is also conceivable.

The combination of DNMT inhibitors and HDAC inhibitors is currently under investigation in several clinical trials. Sequential administration of DNMT inhibitors, such as DAC, followed by the HDAC inhibitor TSA induces optimal re-expression of densely promoter- methylated genes, which cannot be re-expressed by TSA alone (332). This observation suggests a hierarchical organization of the different epigenetic modifications and incites the sequential use of DNMT inhibitors followed by HDAC inhibitors but not the reverse sequence. Interestingly, the sequential administration of DAC followed by different HDAC inhibitors in leukemia cells induces synergistic reexpression of p21, which lacks promoter CpG methylation (333). Apoptotic synergy and DNA damage induction are also observed by the same sequential treatment with consequent p21 upregulation in a p53-dependent fashion. This effect highlights the importance of DNA damage as an off-target effect of epigenetic modifiers in regulating gene expression (48).

Several plant-derived anticancer drugs with epigenetic mechanisms of action have been beneficial and extensively tested in combination treatments with commonly used chemotherapeutic drugs and radiation therapy (Table 4) (156, 172, 177, 191, 209, 213-214, 334-496). Combination regimen of epigenetic modulators with commonly used chemotherapeutic drugs and radiation therapy sensitize the tumors to the anticancer treatment. In fact, epigenetic inactivation of drug sensitivity genes may have occurred in some tumors and these may benefit from the combination therapy (497). In particular, cisplatin combination treatments with plant-derived epigenetic modulators proved beneficial (Table 4); whether epi-drugs sensitize tumor cells to DNA-damage induced apoptosis by cisplatin remains to be determined. Interestingly, antimitotic drugs that stabilize or inhibit microtubules such as the taxane family and vincristine, DNA-intercalating and toposisomerase II inhibitors such as doxorubicin and etoposide, proteasomal inhibitors, arsenic trioxide, tamoxifen, DNA-binding drugs such as cyclophosphamide and oxaliplatin, and nucleotide analogs such as 5-Fluorouracil (5-FU) and gemcitabine showed improved combination treatment response, cytotoxicity, and cell death in a variety of tumors (Table 4). Tumor response was also enhanced in combination treatment of radiation therapy and plant-derived epi-drugs. Nonetheless clinical trials will validate the usefulness of combined epigenetic modulators with commonly used cancer therapeutics.

10. DNA DAMAGE, DNA REPAIR, AND EFFECTS OF PLANT-DERIVED ANTICANCER DRUGS ON CHROMATIN

The integrity of DNA is continuously challenged by different genotoxic agents and environmental stress stimuli which result in the generation of ROS and DNA

Table 4. Combination therapy of major plant-derived anticancer drugs

Purified Plant Compound	Combination with Chemotherapeutic Drug and/or Radiation
Polyphenols	
Anacardic acid	Cisplatin, doxorubicin (172), Ionizing radiation (336)
Curcumin	Ara-C, methotrexate (337), Arsenic trioxide (338), Bacillus Calmette-Guérin (339), Bortezomib (340), Capecitabine (341), Cisplatin (342-345), Cisplatin, doxorubicin (346), Cisplatin, oxaliplatin (347), Dasatinib (348), Docetaxel (156), Doxorubicin (349-350), 5-FU (351-352), 5-FU or 5-FU with oxaliplatin (353-354), Gemcitabine (177, 191, 355-359), Letrozole (360-361), Melphalan (362), Mitomycin C (363), Oxaliplatin (364), Paclitaxel (365-366), Valproic acid (367), Vinblastine (368), Vincristine (369), Gamma-radiation (370), Radiotherapy (371-372), UVA radiation, visible light (373), UVB radiation (374)
(-)-Epigallo-catechin 3-gallate	Bicalutamide (375), Bleomycin (376), Bortezomib (377-378), Cis-platinum(II)diammine dichloride, gamma-radiation (379), Cyclophosphamide (380), Dacarbazine (381), Doxorubicin (382-384), Erlotinib (385-387), IFN-α2β (388), Nonsteroidal anti-inflammatory drugs, selective COX-2 inhibitors (389), Paclitaxel (390), Paclitaxel, vinblastine (391), Retinoic acid (392), Sulindac, tamoxifen (393-394), Sulindac (395-396), Tamoxifen (397-398), Temozolomide (399), Trastuzumab (400), Ionizing radiation (401-402)
Genistein	Amrubicin (403), Ara-C (404), Arsenic trioxide (405), Arsenic trioxide (209, 213-214), Bicalutamide (406), Carmustine (407), Cetuximab (408), Cisplatin (409-412), Cisplatin, docetaxel (413), Cisplatin, docetaxel, doxorubicin (414), Cisplatin, cyclophosphamide, docetaxel, doxorubicin, vincristine, and prednisone (415), Cisplatin, doxorubicin, etoposide (416), Dexamethasone (417), Doxorubicin (418-419), Erlotinib (420), Fludarabine (421), 5-FU (421), Gemcitabine (422), Paclitaxel, vincristine (423), Perifosine (424). Tamoxifen (425-428), Gamma-radiation (335), Photoactivated hypericin (334), Radiotherapy (429-436), X-Rays (437)
Resveratrol	17-allylamino-17-demethoxygeldanamycin (438-439), Ara-C, tiazofurin (440-441), Bortezomib, dexamethasone, fludarabine (442), Bortezomib, perifosine (443), Busulfan, doxorubicin, cycloheximide, gemcitabine, paclitaxel (444), Cisplatin (445-446), Cyclophosphamide (447), Etoposide (448), 5-FU (449-450), Gemcitabine (451), Paclitaxel (452-454), T138067 (455), Vinorelbine Bitartrate (456), Ionizing radiation (457), UVA radiation (458), UVB radiation (459), X-Rays (460)
Alkaloids	
Procainamide	cis-diamminedichloro platinum(II) (461), Cyclophosphamide, methotrexate and 5-FU (462), IFN-α/β (463)
Organosulfur compounds	
Sulforaphane	Arsenic trioxide (464), Cisplatin (465), Doxorubicin (466-467), 5-FU (468), Oxaliplatin (469), Paclitaxel (470), Sorafenib (471), Topical photodynamic therapy (472), X-Rays (473)
Terpenoids	
Parthenolide	Arsenic trioxide (474), Bicalutamide, docetaxel (475), Buthionine sulfoximine (476), Cisplatin (477), Docetaxel (478), Fenretinide (479), L-actacystin (480), NS398 (481), Oxaliplatin (482), Paclitaxel (483-484), Roscovitine (485), Sabarubicin (486), Sulindac (487), Tamoxifen (488-489), Valproic acid (490), Vinorelbine (491), Hyperthermia (492-493), Radiotherapy (494-495), X-Rays (496)

Abbreviations: Ara-C: Arabinoside cytosine; 5-FU: 5-Fluorouracil; IFN: Interferon; UVA: Ultraviolet A; UVB: Ultraviolet B

damage. Following replication and repair, DNA is packaged into chromatin to ensure genomic integrity. The "access-repair-restore" model explains how nucleotide excision repair (NER) functions within the complex chromatin environment (498).

The initial step in the repair mechanism is the removal or remodeling of nucleosomes to permit access to the DNA breaks. Similarly to transcription, which requires transcription factor complexes to access their DNA binding sites, DNA repair also requires chromatin remodeling factors and histone modifying enzymes to access DNA lesions. For instance, the ATP-dependent chromatin remodeling factor (ACF), which contains the SNF2 family member imitation switch (SWI) and Acf1 (499), catalyzes nucleosome movement and changes the nucleosome pattern (500). Another protein, Cockayne syndrome B (CSB), is able to remodel chromatin around DNA lesions, enhancing recruitment of downstream NER factors (501). CSB activity is dependent on both, its histone and DNA binding abilities. Other chromatin remodeling factors include CREB binding protein (CBP) and p300, which interact with the small subunit of the Xeroderma pigmentosum-E damage-specific DNA binding protein (DBB). This physical interaction can cause localized modifications at damaged sites. High mobility group proteins with nucleosomal binding domains further participate in higher-order structure folding (502). Other proteins connecting repair and chromatin are summarized in Green and Almouzni (498).

Ionizing radiation, in addition to endogenous and other exogenous factors, cause double strand breaks (DSBs). DSBs are considered highly genotoxic lesions, and their repair is mediated by two major pathways: homologous recombination (HR) and non-homologous end joining (NHE) (503). One of the earliest detectable epigenetic events in this repair mechanism is the phosphorylation of the histone variant H2AX (504). Although not absolutely required for repair, this phosphorylation precedes the recruitment of repair enzymes such as Rad51 or Rad50 (499) or NBS1 (504), and loss of pH2AX reduces the cell´s ability to cope with DSBs. H2AX phosphorylation modifies the chromatin and permits 'access or action' of repair factors. Histone acetylation is also used during DSB repair. Interestingly, some HATs such as TIP60 do not only acetylate H4 at DSBs, but also have DNA helicase activity, and the large topological changes at DNA caused by helicases could alter DNA-protein contacts. There is evidence that the recruitment of TIP60 to DSBs results in acetylation of pH2AX and removal of pH2AX from chromatin (505). Moreover, there seems to be a close interaction between the different modified histone variants during repair processes (506). Additionally, SWI/SNF, which plays an important role in transcription, has been also directly associated with DSB repair. SWI/SNF deficiency causes increased sensitivity to agents that induce DSBs (507). Following DNA repair, the original chromatin structure has to be restored for the epigenetic modifications to be sustained. One factor potentially involved is the chromatin assembly factor 1 (CAF-1), which plays a role in replication-dependent

chromatin assembly and is immediately recruited to chromatin in UV-damaged cells.

Vorinostat, a synthetic anti-neoplastic HDAC inhibitor drug in clinical use and in several cancer clinical trials, is a potent chromatin modifier. Treatment of colorectal cancer cells with Vorinostat resulted in a massive increase in acetylated H3 and H4, in DNA-damage, and in a deregulation of a panel of DNA repair enzymes (508-509). There are only few examples of plant-derived drugs acting as chromatin modifiers. For instance, parthenolide, although a known NF-kB inhibitor, can modify the chromatin causing cytotoxic effects in cancer cells, independent of NF-kB inactivation (510). It has been shown that NF-kB regulates transcription by binding to regulatory sequences in its target genes and *via* recruitment of co-activators (p300/CBP) or co-repressors (HDAC1). Parthenolide activates ATM and specifically depletes HDAC1 through ubiquitination and proteasomal-mediated degradation, independent of IKK2 and JNK1/2 pathways (326). Curcumin also induces DSBs and is an effective inhibitor of HDAC1 (185). Additionally, anacardic acid is a potent inhibitor of TIP60 HAT activity *in vivo* and sensitizes cells to ionizing radiation (336), suggesting a role for HATs in regulating the DNA damage response. Suppression of p300 HAT activity by anarcadic acid represses UV-induced MMP1 expression and inhibits UV-induced pH2AX and acetyl-H3 levels (168, 511). The isothiocyanate sulforaphane causes DNA damage and chromatin condensation in colorectal cancer cells (512). Polyphenols and caffeic acid induce ROS production by inhibiting scavenger enzymes (513-514). Thus, a relationship between chromatin-modification and the action of plant-derived drugs may be inferred from reports showing pro-oxidant and DNA-damaging effects of these drugs.

11. EPI-DRUG DOSAGE, REVERSIBILITY, AND TARGET SELECTIVITY

A general property of plant-derived anticancer compounds that work through epigenetic mechanisms is their weak inhibition of HDAC and DNMT activities, at pharmacologically achievable concentrations, as compared to other commonly used epi-drugs (213, 327, 515). Hence, high concentrations may be required for their epigenetic activities, possibly eliciting undesired toxicities if administered clinically (48). Such high concentrations may cause acute toxicity in cells resulting in mechanisms, such as general protein degradation, that affect epigenetic as well as other regulators, indiscriminately. Hence, to be deemed epi-drug, a compound should elicit epigenetic activities at concentrations that are not cytotoxic. Demethylating agents, in particular, should not trigger immediate cell death, as do most chemotherapeutic drugs, because the cells must be allowed to divide for the demethylation effect to take place, as previously described for DNA methylation maintenance by DNMT1 (6). Clinical trials have confirmed that low-dose exposures of epi-drugs lead to more effective responses (6). Although plant-derived compounds may be weak HDAC and DNMT inhibitors, their metabolites seem to exhibit epigenetic effects at much lower concentrations than the parent compounds (327). For instance, the sulforaphane metabolite, sulforaphane-cysteine, but not sulforaphane, is able to inhibit HDAC activity in cell-free systems at a low 3-15 μM range(250). It is only when sulforaphane is incubated with cells that inhibition of HDAC activity is observed (250).

Despite the advantage of epi-drugs of being effective at low non-toxic doses, these drugs may elicit transient reversible effects because the deregulated epigenetic patterns may recur after the removal of the drug, allowing the malignant cell population to reappear. Many plant-derived compounds constitute part of the human diet and can have longer lasting epigenetic effects relative to nucleoside analogues (327) and, hence, can be used as epi-drugs that prevent tumor reappearance or even as a natural chemoprevention strategy. Cancer stem cells are hypothesized to be the major reason for tumor recurrence, and the plant-derived parthenolide is the only small molecule, to date, that selectively targets them while sparing normal stem cells (24). Permanent epigenetic silencing in cancer stem cells can replace reversible gene repression, hence, locking these cells into a perpetual state of self-renewal and causing tumor relapses (516). Whether the ability to target cancer stem cells correlates with epi-drug potential is an interesting topic for further investigation.

An important property of some plant-derived compounds is their apparent selectivity towards specific DNMTs and HDACs. Classical DNMT and HDAC regulators, on the other hand, are normally pan-inhibitors probably because they are designed for direct chemical inhibition, which often does not differentiate among isoform targets having similar active sites. Many plant-derived compounds, however, elicit their epigenetic effects not through chemical inhibition but rather by targeting specific signaling pathways. For instance, parthenolide selectively inhibits HDAC1 classes by triggering its proteasomal degradation (326). The epigenetic selectivity of plant-derived compounds may be cell-context dependent but can provide experimental tools that can better help target and understand specific epigenetic effectors. Moreover, such selectivity may prove favorable in some contexts of epigenetic cancer therapy.

Because epi-drugs are used at low doses and may cause transient effects, a combinatorial approach of epigenetic modulators, together, or with commonly used chemotherapeutic or radiotherapeutic treatments, can ensure efficacy of cancer treatment and prevents possible relapse (Table) (517).

12. SUMMARY AND PERSPECTIVES

Accumulating evidence supports the use of epigenetic therapy in cancer chemoprevention and treatment (6). Plant-derived anticancer drugs are at the forefront of drug discovery and have shown promise in epigenetic therapy (22, 162). Plants rich in the secondary metabolites polyphenols, alkaloids, organosulfur

compounds, and terpenoids are rich sources of compounds that target epigenetic mechanisms encompassing histone modifications, DNA methylation, and miRNA regulation. These plant-derived anticancer drugs were shown to target epigenetic pathways in a variety of solid tumors and hematological malignancies. Some of these compounds, such as parthenolide, had their bioavailability increased by the synthesis of more water soluble derivatives, such as dimethyl-amino-parthenolide (518). This emphasizes the importance of compound optimization for some plant-derived anticancer epi-drugs.

Most investigated plant-derived anticancer drugs that target epigenetic mechanisms are modulators of histone acetylation either by altering the activities of HDACs and/or HATs. Genistein causes histone acetylation by inhibiting HDACs and/or activating HATs subsequently activating tumor suppressor genes namely *p53*. Unlike genistein, ECGC causes histone acetylation by inducing HDACs and inhibiting HATs. Curcumin, sulforaphane, and parthenolide decrease HDAC activity but also specifically inhibit HDACs from class I and II. Resveratrol inhibits HAT activity, in particular, p300 but also induces SIRT1 which is associated with decreased acetylation and expression of oncogenes. Histone modifications not only alter the expression of oncogenes and tumor suppressor genes but also of DNA repair and of crucial signaling pathways in tumors such as NF-κB. Histone acetylation mechanisms are extensively studied and many companies have developed HDAC inhibitors programs because of well elucidated chemical and crystal structures of HDACs and inhibitors, such as TSA and sodium butyrate (10). Recently, HATs are rising as drug targets in drug development programs (10, 90). Several plant-derived anticancer compounds such as anacardic acid, curcumin, EGCG, and resveratrol inhibit several HATs, namely p300, PCAF, and Tip60 while curcumin and resveratrol have so far been shown to only inhibit p300. Other histone modifications alter gene expression, and plant-derived anticancer compounds may regulate these pathways and should be the focus of future studies and may result in novel compounds in cancer therapy. In fact, several inhibitors of histone demethylases, methyltransferases, and ubiquitin ligases are at early phases of drug development programs (10). However, some plant-derived compounds, such as curcumin and parthenolide, have poor bioavailability and more water-soluble analogues have been derived with similar or enhanced bioactivity (152, 519). Hence, SAR studies are crucial for optimal use of plant-derived anticancer drugs. Additionally, product standardization is another important step because multiple sources of a given plant can cause discrepancies in the activities of extracted molecules.

Several plant-derived compounds such as EGCG, genistein, procainamide, parthenolide, and several less studied polyphenols such as biochanin A, daidzein, caffeic and chlorogenic acid, catechin, and epicatechin are inhibitors of DNA methylation. These compounds either reduce DNMT activity or specifically inhibit DNMT1, DNMT3a, or DNMT3b and can reactivate silenced tumor suppressor genes leading to tumor growth inhibition, cell cycle arrest, and apoptosis. The direct inhibition of specific DNMTs by plant-derived anticancer drugs results in target selectivity unlike the general DNA demethylating and cytotoxic effects of commonly used nucleoside analogs. Furthermore, chronic administration of nucleoside analogs may result in genome hypomethylation and subsequent chromosomal instability and oncogene activation. In contrast, chronic administration of plant-derived epi-drugs, as part of the human diet, may overcome both, the possibly weak epigenetic activities of plant-derived drugs and the reversibility effects generally associated with epi-drug administration.

The comprehensive analysis of the epigenome and its alteration in cancer will contribute to the development of successful anticancer drugs that work through epigenetic mechanisms (16). Furthermore, miRNA profile in tumor cells will also impact cancer treatment outcome. It remains to be determined whether epi-drugs, specifically those derived from plant resources, modulate miRNA profiles. The development of specific and non toxic epi-drugs that target specific abnormalities of the cancer epigenome is a pressing issue in cancer management, and plant-derived compounds are at the forefront of drug discovery programs. Nonetheless, the challenges facing epi-drug development, whether derived from natural resources or not are similar and should focus on patient and target selection, efficacy in solid and hematological tumors, and whether they target cancer stem cells (10).

Our understanding of the cross-talk between genetic and epigenetics is still unclear, but pharmaco-epigenomics is improving, and the epigenetic strategies to target cancer cells are becoming better defined. Both, inhibition and activation, of counteracting enzymes and processes (HATs/HDACs; DNA methylation/demethylation) are involved in these strategies, by working in concert. An ideal epi-drug will modify histones, such as by increasing their acetylation, in the chromatin around inactive tumor suppressor genes to reactivate them and will modify the chromatin around oncogenes to inhibit them. Equally, such a drug can induce global DNA hypomethylation, which causes chromosomal instability, in cancer but not in normal cells and decrease DNA methylation of promoters of inactivated tumor suppressor genes to reactivate them while causing promoter hypermethylation of oncogenes to reduce their expression. Through this review, which has pooled and analyzed most of the epigenetic mechanisms mediated by plant-derived anticancer drugs, some compounds can be highlighted to possess the characteristics of the ideal epi-drug. These include curcumin and its derivatives, EGCG, genistein, resveratrol and its derivatives, sulforaphane, and parthenolide (Table 1) because they can reactivate tumor suppressor genes and inhibit oncogenes by regulating several epigenetic enzymes and processes. Such anticancer compounds fulfill the criteria of being able to reset the epigenetic twists across the different layers of the epigenome, which we are now starting to understand.

13. LITERATURE SEARCH CRITERIA

The information was collected by searching PubMed, Medline, and EMBASE for articles published

between 1950 and 23 August 2010, including electronic publications available ahead of print. Hence, American, European, and other journals could be retrieved. Literature searches for 'epigenetic mechanisms' and for 'plant-derived compounds' were combined. The former included 'Epigenesis, genetic', 'DNA methylation', 'histone acetyltransferases', 'histone deacetylases', and 'microRNAs' as MeSH terms. The latter included 'plant preparations', 'biological products', 'plant extracts', 'chinese herbal', 'plant oils', 'dietary fiber', 'functional food', 'fruit', 'micronutrients', 'seeds', 'vegetables', and others as MeSH terms. Both searches used explosion search. Then major and minor plant-derived compounds were identified and each searched again using the drug' s name or plant origin as MeSH terms, if available, or as keyword search, otherwise. Full articles were acquired based on titles and abstracts, and references were checked for additional publications. We apologize to those whose work could not be cited.

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Abbreviations: ACF: ATP-dependent chromatin remodeling factor; AMPK: AMP-activated kinase; APE1: Apurinic/apyrimidinic endonuclease-1; Ara-C: Arabinoside cytosine; ATM: ataxia-telangiectasia-mutated; BCL_2: B-cell leukemia/lymphoma 2; BcL-X_L: B-cell leukemia X_L; BMP-2: bone morphogenetic protein 2; BTG3: B-cell translocation gene 3; CACNA2D3: calcium channel related; CBP: CREB-binding protein; CDKI: cyclin dependent kinase inhibitor; COMT: catechol-O-methyltransferase; COX-2: cyclooxygenase 2; CREBBP: cAMP-responsive element binding protein; CSB: Cockayne syndrome B; CTPB: N-(4-chloro-3-trifluoromethyl-phenyl)-2-ethoxy-6-pentadecyl-benzamide; CYLD: cylindromatosis; DAB: Dimethylaminoazobenzene; DAPK: death-associated protein kinase; ER: estrogen receptor; DIABLO: direct IAP binding protein with low pI; DNMT: DNA methyltransferase; DNMT3L: DNMT3 like protein; ds: double strand; DSB: double strand breaks; EGCG: (-)-epigallo-catechin-3-gallate; 5-FU: 5-Fluorouracil; ERG: E-twenty six related gene; FOXO3a: forkhead homeobox type O 3a; GATA-5: transcription factor; G6Pase: glucose-6-phosphatase; GSTP1: glutathione S-transferase P 1; HAT: histone acetyltransferase; HDAC: histone

deacetylase; HIN-1: high in normal-1; 5-hmc: 5-hydroxymethylcytosine; hMLH1: human mutL homolog 1; HR: homologous recombination*;* hTERT: human telomerase reverse transcriptase; IL-6: interleukin-6; IFN: Interferon; IKK: IκB kinase; JMJD6: Jumanji domain-containing protein 6; 5-mc: 5-methyl-cytosine; LSD1: lysine specific demethylase; MAO: monoamine oxidase; MCM: minichromosome maintenance; MDR1*:* multidrug resistant protein 1; MGMT: O^6- methylguanine-DNA methyltransferase; miR: micro RNA; MMP9*:* matrix metallopeptidase 9; MTA1: Metastasis-associated protein 1; NAD: nicotinamine adenine dinucleotide; NER; nucleotide excision repair; NF-κB: nuclear factor kappa B; NKX-3.1: a homeobox gene; PCAF: P300/CBP-associated factor; Pepck*:* phosphoenolpyruvate carboxykinase; Pgc-1α: peroxisome proliferator-activated receptor γ coactivator 1α; PKC: protein kinase C; PP: protein phosphatase; PRC2: polycomb repressive complex 2; PRMT: protein arginine methyltransferase; PSA: prostate specific antigen; PTEN: phosphatase and tensin homolog; RAR: retinoic acid receptor; RASSF1A: ras-association domain family 1 A; RECK: reversion-inducing cysteine-rich protein with Kazal motifs; RNAi: RNA interference; ROS: reactive oxygen species; SAH: S-adenosyl-L-homocysteine; SAMC: S – Allylmercaptocysteine; SAR: structure activity relationship; Sir2: silent information regulator 2; siRNA: small interfering RNA; SIRT1: sirtuin 1; SP1: stimulating protein 1; SUMO: small ubiquitin-related modifier; SWI: SNF2 family member imitation switch; TIP60: TBP interacting protein; tRNA: transfer RNA; TSA: trichostatin A; TSC22: transforming growth factor-simulated clone-22; UVA/B: Ultraviolet A/B; WIF-1: Wnt inhibitory factor 1; ZBG: zinc binding group

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