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REVIEW ARTICLE

Anticancer Natural Compounds as Epigenetic Modulators of Gene Expression

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Abstract: Accumulating evidence shows that hallmarks of cancer include: "genetic and epigenetic alterations leading to inactivation of cancer suppressors, overexpression of oncogenes, deregulation of intracellular signaling cascades, alterations of cancer cell metabolism, failure to undergo cancer cell death, induction of epithelial to mesenchymal transition, invasiveness, metastasis, deregulation of immune response and changes in cancer microenvironment, which underpin cancer development". Natural compounds as bioactive ingredients isolated from natural sources (plants, fungi, marine life forms) have revolutionized the field of anticancer therapeutics and rapid developments in preclinical studies are encouraging. Natural compounds could affect the epigenetic molecular mechanisms that modulate gene expression, as well as DNA damage and repair mechanisms. The current review will describe the latest achievements in using naturally produced compounds targeting epigenetic regulators and modulators of gene transcription *in vitro* and *in vivo* to generate novel anticancer therapeutics.

Keywords: Chromatin, DNA methylation, Epigenetics, Histone acetylation, Histone methylation, microRNA, Natural compounds, Tumorigenesis.

1. INTRODUCTION

The Hallmarks of Cancer perspective presents an organizing appreciation of human cancer complexity of human cancers, and understanding of the aberrant basis of this proliferative disease [1-3]. This set of tumor-associated alterations underline molecular and cellular events that are necessary to support tumor initiation and progression [1-3]. They include: "sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, avoiding immune destruction, cancer-promoting inflammation, genome instability and mutation, and deregulating cellular energetics" [1-3]. The additional molecular mechanisms underlying these tumor-specific alterations include genetic and epigenetic changes in the cancerous cells [1-5]. Tumor tissue microenvironment (e.g. endothelial cells infiltrating immune cells, and activated cancer-associated fibroblasts) has been recently added to these tumor-related traits ("hallmarks") [6]. The hallmark concept suggests novel venues to generate new ideas and approaches leading to potentially beneficial therapeutics involving targeting multiple cancer cell functions, now being explored in pre-clinical and clinical trials [1-6].

Genomic instability is often associated with the alterations in DNA regions encoding oncogenes, tumor suppressor genes, as well as DNA repair genes [1, 7, 8]. Both genetic and epigenetic alterations are arising from exposure to exogenous and endogenous stress agents leading to DNA and chromatin damage and deregulated gene expression and resulting in non-functional proteins that underlie tumor initiation and progression [4, 5, 8-10]. A plethora of epigenetic changes including DNA methylation, post-translational histone modifications, and chromatin-binding proteins, microRNA modulation constitute a regulatory network needed for controlling gene transcription and RNA processing, DNA replication, DNA damage repair, as extensively reviewed elsewhere [11-39].

Accumulating evidence from the global genome sequencing and expression studies emphasizes the role for genetic and epigenetic alterations leading to inactivation of cancer suppressor genes, overexpression of oncogenes, modification and modulation of transcription factors, chromatin and epigenetic regulators leading to a deregulation of multiple intracellular signaling cascades, and subsequently to cancer development [4, 9, 20, 23, 27, 36]. Because of cancer heterogeneity, new layers of regulation have been added into a complex molecular network leading to carcinogenesis and

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cancer progression [6]. "Epigenetics" is defined as a pattern of heritable changes in chromatin DNA and protein modifications leading to an altered expression of multiple target genes involved in cell cycle arrest, apoptosis, autophagy, DNA damage response, oxidative metabolism [12, 14, 21, 37, 39]. Recently, epigenetic DNA and protein post-translational modifications (PTM, e.g. phosphorylation, acetylation, methylation) were shown to largely contribute to the initiation and progression of cancer [12, 20, 21, 23]. On the one hand, a hypermethylation of specific DNA associated with gene promoter regions causes silencing of tumor suppressor genes, leading to inactivation of these genes in cancer cells [10, 14, 16, 20-23, 30, 32-36]. At the same time, demethylation of DNA promoter sequences of genes inducing cancer (oncogenes) leads to their overexpression and initiation or progression of cancer [10, 14, 16, 20-23, 30, 32-36]. Changes in chromatin structure, architecture and dynamics, as well as alterations in the transcription factors dramatically influence the expression of target genes by either activating or inactivating their transcription [11, 17, 18, 25, 29, 30-33].

Gene expression is mostly controlled at the level of the transcription [40-45]. Transcription control regions of protein-encoding genes include: the core promoter, where RNA polymerase II binds, the proximal and distal promoter, responsible for gene expression regulation, and the enhancers and silencers [40-42]. Activation of gene expression depends on the binding of specific transcription factors to regulatory promoter DNA elements in target genes, subsequently recruiting the transcription accessory proteins (e.g. Mediator complex, general transcription factors, etc.) leading to an assembly of the transcription pre-initiation complex, as reviewed in [40-45]. Transcription factors ultimately transduce the proliferation signals from the cell membrane elicited by growth factors, and other extracellular signals and stress signals through multistep upstream signaling pathways originated in cytoplasm into the nuclei [45, 46]. Many human oncogenes encode for transcription factors or chromatin-associated regulators, which are overexpressed in human cancers (e.g., JUN, FOS, MYB, MYC, NOTCH, MLL, MTA1, REL, SOX9, STAT, TWIST, E2F, ERG, SMAD, WT1), as reviewed in [46-58]. Tumor suppressors (e.g. TP53 family members, F-Box and WD repeat domain containing-7 protein FBXW7, Forkhead transcription factors, ETS transcription factor MEF [ELF4], RECK, SOX10) are transcription factors, as well [54-66].

Epigenetic modifications are potentially reversible, thereby making them highly interesting targets for novel anticancer therapeutics [11-39]. The main molecular events responsible for epigenetic regulation of gene expression are: DNA methylation, methylation and acetylation of chromatin histone and non-histone proteins, chromatin assembly and disassembly, and post-transcriptional gene regulation by non-coding RNAs [11-39]. The human genomic DNA exists and function in packaged forms of chromatin, a macromolecular DNA-protein complex containing DNA, histone and non-histone proteins [4, 31, 45]. Chromatin consists of repeating units called "nucleosomes" [4, 31, 45]. Epigenetic alterations affecting gene expression outcome are regulated by direct chemical modification of chromatin, including DNA methylation and PTMs (known as histone code) of the N-terminal histone tails that protrude from the nucleosome structures [17, 31, 45]. Specific histone tails are the targets of various PTMs, including acetylation, methylation, phosphorylation, ubiquitination, sumoylation and ADP ribosylation [17, 29, 30, 32, 45]. Epigenetic changes are also modulated by non-coding microRNAs (e.g. microRNAs), as reviewed elsewhere [19, 24, 25, 28, 67-79]. Global epigenetic alterations are a hallmark of cancer [1-5, 80, 81]. Cancer epigenetics revealed the deregulation of all components of the epigenetic machinery including DNA methylation, histone modifications, chromatin structure, and non-coding RNAs [12, 17, 22, 80, 81]. Since the epigenetic modifications are reversible and precisely regulated by epigenetic enzymes the modulation of the latter could modulate the transcription of tumor suppressive and tumor promoting genes [80, 81]. Many epigenetic alterations are associated with aberrations in the expression and/or activity of epigenetic enzymes [80, 81]. These are the key reasons why epigenetic enzymes, regulators and modulators have recently emerged as prime targets for anticancer chemotherapy [11, 12, 23, 81, 82]. Drugs targeting epigenetic processes are at the forefront of anticancer chemotherapeutic strategy, and plant-derived compounds (natural compounds) have shown a great promise [83-97].

Epigenetic-driven changes in gene expression could be altered by various endogenous factors including nutrients, as well as by exogenous environmental factors [85, 86, 98, 99]. Potential anticancer natural compounds have been shown causing epigenetic alterations and facilitating the inhibition of cancer growth [83-97, 100]. Natural compounds have been reported to modulate several epigenetic modification processes known to underlie the molecular mechanisms involved in tumorigenesis, such as DNA methylation, histone modifications (methylation, acetylation and phosphorylation), and non-coding microRNA expression [83-97]. Numerous natural compounds from various plants, fungi and marine organisms showed the ability of altering epigenetic make-up of cancer cells through their epigenetic targets [83-100]. Natural compounds have been reported to repair DNA damage by enhancing histone acetylation and affecting the promoter DNA methylation thereby modulating multiple cell death pathways [88].

TRANSCRIPTION FACTORS AND NATURAL COMPOUNDS

When the genome stability is severely affected upon multiple challenges from environmental stresses, the excessive genomic damages cause increased frequencies of mutation and/or epigenetic alterations of oncogenes and tumor suppressors disrupting cellular homeostasis and leading to neoplastic transformation [85, 86, 98, 99]. Genetic and epigenetic changes (DNA hypermethylation, histone deacetylation/acetylation, histone methylation/demethylation and microRNA targeting) of tumor suppressive genes result in their inactivation, as well as in amplification/overexpression of oncogenes, which subsequently leads to initiation and progression, of cancer [9, 10, 13, 14, 23, 26, 69, 72, 80, 81]. Tumor suppressor "driver" genes include: genes for retinoblastoma protein (*RB*), tumor protein p53 (TP53), *BRCA1* and *2, PTEN, VHL, APC, CD95, ST5, 7* and *14, YPEL3*, whereas "driver" oncogenes include: growth factors

(e.g. *c-SIS, WNT*), receptor tyrosine kinases (*EGFR, PDGFR, VEGFR, TRK, ERBB2*), cytoplasmic tyrosine (*SRC, ABL,* and *BTK*) and serine/threonine (*ATM, MTOR, ERK, PI3KCA, AKT1, 2 and 3, LKB1,* and *RAF*) kinases, transcriptional factors (*MYC, E2F*), GTP hydrolases (*RAS*), and others (*CCND1, CLND1A*), as reviewed [85, 101].

Deregulated expression of transcription factors plays a critical role in various human cancers. Since their activities are tightly regulated, these proteins could acts as highly promising anticancer drug targets. A number of oncogenic transcription factors, such as Activator Protein 1 (AP-1), Inhibitor of Differentiation 4 (ID4), Nuclear Factor-kappaB (NF-κB)/REL-A, and Signal Transducer and Activator of Transcription (STAT)-3, 5 and 6, MYC, Runt-related transcription factor (RUNX)-1, NOTCH1-4, CCAAT/Enhancer Binding Protein alpha (C/EBPα), β-catenin (CTNNB1), Sterol Regulatory Element-Binding Protein (SREBP)-1c, members of Tumor Protein (TP)-p53 family Interferon Regulatory Factor (IRF)-5, SMAD4, GLI factors, Krüppel-Like Factor (KLF)-5, MIcrophthalmia-associated Transcription Factor (MITF), PAX family members, TWIST, and Wilms' Tumor (WT)-1 factor are induced in many human cancers and thus may present promising targets for cancer prevention [45, 54, 101]. For example, MYC functions as a transcriptional regulator for many human genes, which correlates with the ability of several transcription-interfering drugs to kill cancer cells. Additionally, inhibition of NF-κB in parallel could strongly enhance the apoptotic potential of the chemotherapy and often overcome an inducible chemoresistance. Accumulating evidence suggests that many natural compounds could potentially affect the tumor cell survival through targeting specific transcriptional factors [102-108].

Curcumin (diferuloylmethane), a polyphenol from *Curcuma longa*, was shown to inhibit tumor cell growth and induce tumor cell death. Curcumin was reported modulating various signaling pathways implicated in inflammation, proliferation, invasion, survival, and apoptosis [109-111]. Curcumin was shown to induce TP63 and MYC-Associated factor X (MAX), as well as to inhibit NF-κB in hepatocarcinoma cells, and OCT4 in placenta pluripotent embryonic carcinoma cells (NCCIT) suggesting that these genes could act as potential therapeutic targets, especially for cancer stem cells [112, 113]. Recently, curcumin was found to inhibit the activity of NF-κB and NOTCH1 in human hematopoietic Raji cells of hematopoietic origin by inhibition of Histone DeACetylase (e.g. HDAC1, HDAC3) interacting with E1A binding Protein 300 (EP300) and cAMP response element-binding factor (CREB)-binding protein (CREBBP or CBP) co-activators, subsequently resulting in inhibition of cell proliferation [113]. Curcumin was also found to modulate the expression of AP-1 transcription factor components, c-FOS and c-JUN [114-118]. Curcumin (at 40 and 80 μM) induced DNA damage, increased ratio between TAp73 proteins with the transactivation domain (TA-) and without it (ΔN-), and led to apoptosis in the TP73 overexpressing and p53-deficient human hepatoma Hep3B cells [119].

Tea polyphenols isolated from green tea *Camellia sinensis* are: [−]-epicatechin, [−]-epicatechin-3-gallate, [−]-epigallocatechin, and [−]-epigallocatechin-3-gallate (EGCG). The major polyphenols in black tea are: catechins, flavanols, methylxanthines, theaflavins and thearubigens [120]. Black tea compound Polyphenon-B abrogated the growth of rat hepatocellular carcinomas (induced by 3,3'-Diaminobenzidine), while decreasing the hypoxia-inducible factor (HIF)-1α expression and increasing HDAC1 levels [121]. Epicatechin gallate induced a tumor cell death via TP53 activation and stimulation of p38 Mitogen-Activated Protein Kinase (MAPK) and c-Jun N-terminal kinases (JNK) in human colon cancer SW480 cells [122].

Transcription factors (e.g. NF-κB, AP-1, activating transcription factor 2, CREB, and HIF-1α) were downregulated in mouse melanoma cells upon treatment with the combination of epigallocatechin-3-gallate and dacarbazine, or quercetin with sulforaphane [123-126]. Curcumin and EGCG were shown inhibiting the cancer stem cell phenotype of breast cancer cell lines (MDA-MB-231 and MCF-7) via down-regulation of STAT3 and NF-κB signaling [127]. Human pancreatic cancer xenografts when treated with the Traditional Chinese Medicinal (TCM) formula "Qingyi-huaji" exhibited a decrease of NOTCH4 and JAG1 expression and enhanced the antitumor activity of gemcitabine [128]. Similarly, BDL301 (TCM) was reported to inhibit tumor cell proliferation by modulating STAT3 pathway leading to apoptosis in human colorectal cancer cells [129]. Isoprenoid Ascochlorin was found to inhibit growth and invasion of hepatocellular carcinoma by targeting STAT3 signaling through the induction of protein inhibitor of activated STAT3 [130]. A sesquiterpene lactone Alantolactone was shown to selectively suppress the STAT3 activation exhibiting a potent anticancer activity in breast cancer MDA-MB-231 cells and colorectal HepG2 cells [131, 132]. Ethyl acetate extract from *Jiedu Xiaozheng Yin* was reported to inhibit the proliferation of human hepatocellular carcinoma cells *in vitro* and *in vivo* by suppressing the polycomb complex member BMI1 (also known as polycomb group RING finger protein 4, PCGF4) or RING finger protein 51, RNF51) and CTNNB1 (β-catenin) signaling [133, 134].

Nuclear factor erythroid-2 (NF-E2)-Related Factor 2 (NRF2), a transcription factor regulating antioxidant defense, is activated by sulfur-containing dietary phytochemicals, phenethyl isothiocyanate and sulforaphane [135-146]. This activation occurs through the phosphorylation of Extracellular signal-Regulated Kinase (ERK) and JNK protein kinases leading to a subsequent phosphorylation and nuclear localization of NRF2 protein [145]. EGCG induced nuclear accumulation and transcriptional activity of NRF2, as well as binding of NRF2 to the antioxidant response element sequence located at the target gene promoters in human MCF10A breast epithelial cells [142-146]. Indole-3-carbinol purified from the brassica genus of he cruciferous vegetable family (*Brassicaceae*), including broccoli, cabbage, cauliflower, mustard and radish, as reviewed in [147-150]. In acidic environment of stomach, indole-3-carbinol is transformed into diindolylmethane condensation compounds. Both indole-3-carbinol and diindolylmethane induced apoptosis in various cancer cell lines by modulating nuclear receptor-mediated signaling [147-150]. Indole-3-carbinol suppresses NF-κB activity and stimulates the TP53-dependent pathway and its downstream target genes encoding TP53 Upregulated Modulator of Apoptosis (PUMA), Phorbol-12-Myristate-13-Acetate-Induced Protein (PMAIP)-1, and

Apoptotic Protease Activating Factor (APAF)-1 in pre-B acute lymphoblastic leukemia cells [150].

Resveratrol [3, 5, 4'-trihydroxy-trans-stilbene] is a natural polyphenol from blueberries, mulberries, cranberries, peanuts and grapes. Resveratrol was shown to display marked anti-cancer potential [151]. Resveratrol blocks the HIF1α-mediated androgen receptor signaling and reduces proliferation of prostate cancer cells *in vitro* and tumor progression *in vivo* [152, 153]. *In vivo* study indicated that resveratrol inhibits the growth and development of pancreatic cancer in *LSL K-ras G12D* mice (carrying a latent point-mutant allele of *Kras2* [*K-rasG12D*]), as well as the self-renewal capacity of pancreatic cancer stem cells derived from human primary tumors [154]. Resveratrol was found to induce apoptosis of human cancer stem cells by activating capase-3/7 and inhibiting the expression of BCL-2 and XIAP proteins [154, 155]. Pluripotency maintaining transcription factors (e.g. NANOG, SOX2, c-MYC and OCT4) were inhibited by resveratrol, curcumin and epigallocatechin-3-gallate in human cancer stem cells [154-157]. Cucurbitacin B from *Hemsleya endecaphylla* decreases tumor cell proliferation and induces apoptosis through modulation of STAT3 pathway in human lung cancer A549 cells [158]. Guassinoid from *Eurycoma longifolia Jack*, eurycomanone, was reported to inhibit Jurkat and K562 cell viability and proliferation without affecting healthy cells [159, 160]. Interestingly, eurycomanone inhibited NF-κB signaling through inhibition of IκBα phosphorylation and upstream mitogen activated protein kinase signaling [159, 160].

Aaptamines from the marine sponge *Aaptos sp*. decrease proliferation of various human cancer cells through a modulation of AP-1, NF-κB, and TP53-dependent transcriptional activities [161]. Codonolactone, a sesquiterpene lactone from *Chloranthus henryi Hemsl*, inhibits cancer cell invasion, migration and metastasis of breast cancer cells by downregulating the transcriptional activity of RUNX2 [162]. Hirsutine from *Uncaria rhynchophylla* is an anti-metastatic phytochemical, which inhibits breast cancer cell invasion by targeting NF-κB activation [163]. Chebulagic acid from *Terminalia chebula* induces G1 arrest, decreases NF-κB level and activity, and promotes apoptosis in human retinoblastoma cells [164, 165]. Bergamottin, a natural furanocoumarin from grapefruit juice, induces apoptotic cell death in human multiple myeloma cells through the inhibition of STAT3 signaling [166]. The ethyl acetate extract of *Annona muricata* induced cell cycle arrest and apoptosis in A549 cells through activation of the mitochondrial-mediated signaling and suppressing nuclear translocation of NF-κB [167]. Isocudraxanthone K from *Cudrania tricuspidata* induces growth inhibition and apoptosis, as well as a phosphorylation of AKT, p38 MAPK, and ERK, as well as downregulation of HIF-1α in oral cancer cells [167, 168].

Ethanolic extracts of *Piriformospora indica* roots markedly upregulated the TP53 protein expression in human nasopharyngeal carcinoma cells (NPC-TW 01 and NPC-TW 04) in a time- and dose-dependent manner [169]. Grifolin from the mushroom *Albatrellus confluens* has been shown to induce cell cycle arrest in various human cancer cells by targeting extracellular signal-regulated kinase 1 or by upregulating Death-Associated Protein Kinase (DAPK)-1 via TP53 transcriptional regulation [170]. Chalcones (1,3-diphenyl-2-propen-1-ones), naturally-occurring compounds from spices, tea, beer, fruits and vegetables, were shown to modulate transcription factors in key pathways or molecular targets in cancers, including TP53, NF-κB, STAT3, AP-1, NRF2, and CTNNB1/WNT [171]. A herbal carbazole alkaloid mahanine was found to upregulate and activate TP53 protein leading to a reactive oxygen species-mediated nuclear accumulation of Phosphatase and TENsin homolog (PTEN) and its interaction with TP53/TP73 proteins in colorectal cancer cells, as well as to inhibit the STAT3 expression in cervical cancer cells [172, 173].

Dehydroleucodine, a sesquiterpene from *Gynoxys verrucosa Wedd* (Ecuador), induced cell cycle arrest, apoptosis and DNA damage in human astrocytoma D384 cells [174]. The cell death resulted in the increased expression of Cyclin-Dependent Kinase iNhibitor (CDKN1A) and BAX proteins, and was likely to be initiated by phosphorylation of TP53, TP73, and γ-H2AX proteins in D384 cells exposed to dehydroleucodine [174]. Treatment of radiation-exposed human cervical cancer cells with diallyl disulfide (DADS, extracted from crushed garlic *Allium genus*), resulted in decrease in cell viability and increased radiosensitivity, as described elsewhere [175]. Furthermore, a combination DADS with radiation activated apoptosis pathways and expression of TAp73, and its downstream proteins (e.g. tumor necrosis factor ligand superfamily member 6, also known as FASLG, and Apoptotic protease activating factor-1, APAF1), as indicated in [175]. Flavaglines (rocaglamide and silvestrol) were reported to target primitive human leukemia cells and enhance anti-leukemia drug activity via MYC inhibition and the disruption of mitochondrial integrity [176]. On the other hand, rocaglamide was found to protect nonmalignant primary cells from DNA damage-induced toxicity through inhibition of TP53 protein synthesis [177].

DNA METHYLATION AND NATURAL COMPOUNDS

DNA methylation of gene promoters is often inversely correlates with gene expression [178-185]. Multiple molecular mechanisms underlie the DNA methylation-mediated transcriptional silencing [16, 22, 27, 30, 33, 36, 186-194]. Transcription factors, including CREB, E2F, NF-κB and AP-2, failed to recognize specific sequences after methylation [194-209]. However, the Methyl-CpG-Binding Domain (MBD) proteins bound to the methylated promoter sequences and thereby also prevent the transcriptional factor to interact with promoter DNA [188, 198, 202]. MBD proteins were shown to recruit HDACs and histone methyltransferases [205, 207, 210-215]. Numerous studies report the role for global hypomethylation/hypermethylation of specific promoter regions of tumor suppressor genes in development of cancer [80, 81]. Whole-genome technologies found that the promoter DNA hypomethylation can activate genes involved in tumor cell metastasis, and invasiveness [9, 15, 16, 23, 27, 30, 36, 186, 189].

DNA methylation is process to directly regulate gene transcription by altering nucleosome packaging of DNA and essentially preventing the binding of RNA polymerase to transcription starting site [82, 189, 198, 216-218]. DNA methylation is catalyzed by DNA methyltransferase

(DNMT) transferring methyl groups from S-adenosyl-L-methionine (SAM) to a cytosine present next to guanine, known as CpG island, forming 5'-methylcytosine-guanine dimers. In mammalian cells, DNMT1, DNMT3A and DNMT3B add methyl group to the 5' position of the cytosine ring, forming 5-methyl cytosine within the promoter sequence enriched with CpG dinucleotide islands [219-223]. The gene promoter and intron areas are enriched with CpG islands serving as regulatory elements of gene expression [219-224]. DNMT1 is responsible for existing methylation patterns following DNA replication by adding methyl groups to corresponding daughter DNA strands [225-236]. However, DNMT3A and DNMT3B preferentially target unmethylated CpG sites to initiate de novo methylation [225-236].

"In humans, ~70% of all CpG islands are methylated, primarily in the heterochromatin" (transcriptionally-inactive chromatin DNA), thereby serving as markers for gene silencing [14, 237, 238]. In contrast, euchromatin (transcriptionally-active chromatin DNA) CpG islands are free from methylation, therefore providing access to enzymes and regulators of transcription, such as RNA polymerase, transcription factors and chromatin-associated proteins [14, 237, 238]. In cancer cells, global hypomethylation often causes reactivation of various oncogenes, and imbalance between widespread DNA hypomethylation and regional hypermethylation may play significant role in tumor initiation and progression [223, 224, 239-243]. Hypermethylation of CpG islands within the promoter region DNA of tumor suppressor genes could also increase the tumorigenesis causing transcriptional silencing of these genes [4-6, 22, 27, 30, 35, 39]. Inhibitors of DNMTs (5-azacytidine (Vidaza) and 5-aza-2′-deoxycytidine (Dacogen, or decitabine) are currently under clinical evaluation for the treatment of acute myeloid leukemia [243, 244].

In addition to regulation of gene expression by DNA methylation, MBD proteins can bind to the methylated cytosine [198, 245-249]. Up to date, six methyl-CpG binding proteins (e.g. MECP2, MBD1, MBD2, MBD3, MBD4 and KAISO [ZBTB33]) were found acting as transcription repressors in mammalian cells [24, 248]. Usually MBD proteins contain MBD at the amino terminus and a transcription repression domain in the central domain. However, the KAISO protein is lacking an MBD domain, and binds methylated CGCG sequence through its zinc-finger domain. Various MBD proteins may recruit co-repressor complex, including HDACs leading to chromatin compaction, which results in transcriptional repression of genes [211, 212]. A number of genes implicated in regulation of DNA repair (e.g. *MLH1, MGMT*) cell cycle arrest (e.g. *CDKN2A CDKN2B, ARF*), apoptosis (e.g. *DAPK1* and *2*), drug detoxification (e.g. *GSTP1* encoding glutathione S-transferase P), are inactivated by this epigenetic alteration [27, 30, 33, 35, 189, 191, 250]. In addition for being transcriptional repressor, the MBD2 protein exhibits demethylase activity *in vitro* [251-262].

Many natural compounds, particularly flavonoids, are shown to alter epigenetic-driven regulation of gene expression in tumor cells. Flavonoids are natural phenol compounds that form a large group of secondary plant metabolites with interesting biological activities. They can be categorized into six major subclasses (flavan-3-ols, flavonols, flavones, flavanones, isoflavones, and anthocyanidins), which display diverse properties affecting modulation of the DNA methylation status and histone acetylation [263-266]. Flavonoids, a large group (more than 5000 compounds) of secondary natural compounds, are widely distributed throughout the plant kingdom (e.g. parsley, blueberries, black tea, citrus, wine, cocoa, peanuts, etc.), as reviewed elsewhere [263, 265]. Flavonoids were shown to exert cytostatic and apoptotic activities toward tumor cells [263-268]. These biological activities are likely to be supported various molecular mechanisms (e.g. modulation of the activities of phase I/II detoxification enzymes, antioxidant activities, inhibition of protein kinases, cell cycle arrest, modulation of gene transcription via epigenetic modifications), as reviewed in [263-268]. For example, anthocyanins/anthocyanidins from black raspberries inhibited DNMT1 and reactivated tumor suppressor genes by demethylating their promoter DNA regions [269].

A number of studies reported inhibitory effects of tea polyphenols on DNA methylation in ovarian, oral, esophageal, breast, gastric, prostate, skin, colorectal, pancreatic, and head and neck cancers [87, 270-277]. Structural and molecular modeling studies suggested that D- and B-ring structures of tea polyphenols (e.g. EGCG) are important for their inhibitory effects on DNMT activity [267]. EGCG was shown to bind Pro-1223, Glu-1265, Cys-1225, Ser-1229, and Arg-1309 within the DNMT protein catalytic pocket [267, 278]. Additionally, catechol-containing polyphenols inhibit DNMTs through: (a) an increasing of the SAM o-methylation by the catechol-O-methyltransferase enzyme; (b) direct inhibiting the activity of dihydrofolate reductase enzyme, disrupting the folate cycle and increasing SAM levels; and (c) directly inhibiting DNMTs, independent of methylation status [267, 278].

Inhibition of DNMTs by tea catechins and bioflavonoids ultimately results in DNA hypomethylation and re-expression of repressed genes [278]. Studies indicated that the inhibitory effect of tea polyphenols on cancer cells might be associated with their ability to reactivate tumor suppressor genes by promoter demethylation [278]. EGCG has been reported to reverse the hypermethylation of *CDKN2A*, Retinoic Acid Receptor-β (*RARβ*), O^6-MethylGuanine DNA MethylTransferase (*MGMT*), and MutL Homolog-1 (*MLH1*) genes through suppression of DNMT1 activity in human esophageal cancer KYSE 510 cells by binding to the DNMT1 catalytic pocket and inhibiting its enzyme activity [279]. EGCG was found to inhibit DNMT activity and reactivate methylation-silenced RARβ gene in human colon and prostate cancer cells [267]. EGCG was shown to demethylate the promoter DNA regions of genes encoding Annexin A1 (*ANXA1*) and Wnt Inhibitory Factor 1 (*WIF1*) in lung cancer cells [280-282]. Exposure of human epidermoid carcinoma A431 cells to EGCG treatment decreased global DNA methylation levels, as well as the levels of 5-methylcytosine, DNMT activity, and DNMT1, DNMT3A and DNMT3B proteins [283]. At the same time, EGCG was also found to reactivate silenced tumor suppressor genes, *CDKN1A* and *CDKN2A* in A431 cells [283]. EGCG was reported to partially reverse the hypermethylation status of the *RECK* (REversion-inducing-Cysteine-rich protein with Kazal motifs) gene, a novel tumor and metastasis suppressor

gene, which controls matrix metalloproteinases and inhibits tumor invasiveness [65, 284]. Enhanced RECK expression, as well as decreased levels for matrix metalloproteinases 2 and 9 were observed in oral squamous cell carcinoma cell lines after treatment with EGCG [284]. Green tea treatment markedly inhibited CpG methylation of the *RXRα* and TElomerase Reverse Transcriptase (*TERT*) gene promoter DNA regions [285, 286]. Green tea polyphenol EGCG treatment reduced HDAC and DNMT protein levels in methylation-sensitive HCT 116 human colon cancer cells [287]. Similar effects were shown in esophageal, oral, skin, lung, breast and prostate cancer cells suggesting the potential molecular mechanism for green tea anticancer effects [270].

Soy flavonoids, genistein, biochanin A and daidzein, were shown to reverse DNA hypermethylation of *CDKN2A, RARβ,* and *MGMT* genes in human esophageal squamous KYSE 510 carcinoma cells, as well as *RARβ* gene in human prostate cancer LNCaP and PC-3 cells. This effect was correlated with inhibition of DNMT1, 3A and 3B [288]. Non-toxic concentrations of genistein induced demethylation of the *GSTP1* gene promoter DNA regions, which led to a restoration of its expression in human breast cancer MDA-MB-468 cells [289]. Genistein exposure was shown to demethylate the promoter region DNA of *BTG3* tumor suppressor gene, whose expression was downregulated in renal cancer, by inhibiting the activity of DNMT1 and MBD2 in renal cell carcinoma A498 cells [290]. Human colon cancer SW1116 cells treated with genistein exhibited induced *WNT5A* gene expression and decreased methylation of CpG islands on its promoter DNA regions, as well as reduced tumor cell proliferation [291, 292]. Flavonol quercetin from citrus fruits and buckwheat inhibited the proliferation of colon cancer RKO cells by reversing hypermethylation of the *CDKN2A* gene promoter DNA [293, 294].

In silico studies showed that curcumin could covalently block the catalytic thiol group at the C1226 binding site of DNMT1 [295]. Curcumin was found to induce global hypomethylation, as well sequence-specific demethylation at promoter DNA regions of epigenetically silenced genes in human leukemia MV4-11 cells [296]. Mouse *Nrf2* gene was epigenetically silenced during the progression of prostate tumorigenesis in TRAMP mice [297]. Curcumin reversed the methylation status of the first 5 CpG islands in the promoter DNA region of the mouse *Nrf2* gene [298]. Curcumin treatment restored expression of human *NEUROG1* gene encoding neurogenin 1 in prostate cancer LNCaP cells by demethylating the first fourteen CpG sites within its promoter DNA [299]. Curcumin also reduced MECP2 binding to the human *NEUROG1* gene promoter DNA sequences [299]. Treatment with curcumin increased HDAC1, 4, 5, and 8 levels, but decreased HDAC3 expression. HDAC activity, H3K27me3 levels, binding at the *NEUROG1* promoter DNA region was decreased after treatment, suggesting ability of curcumin to re-express yet another gene silenced by epigenetic modification in cancer [299]. Curcumin induced demethylation of the *RARβ2* gene promoter DNA sequence, and subsequently reactivation of this gene in SiHa cervical squamous cell carcinoma cells and HeLa cervical adenocarcinoma cells [300].

Hydrolysis of these glucosinolates from *Brassicaceae* (known as cruciferous vegetables, such as e.g. cauliflower, cabbage, garden cress, bok choy, broccoli, brussels sprouts) by myrosinase generates biologically active isothiocyanates (sulforaphane, phenethyl isothiocyanate), and indoles [301-303]. Sulforaphane exhibits anti-carcinogenic activity, enhances xenobiotic metabolism, induces cell cycle arrest, and apoptosis in human cancer cells [304]. Sulforaphane decreased DNMT1 and DNMT3A enzymatic activities and demethylated the human *TERT* gene first exon in human colon cancer CaCo-2 cells and breast cancer MCF-7 and MDA-MB-231 cells [305, 306]. Sulforaphane and 3,3'-diindolylmethane were found to induce re-expression of tumor suppressor genes silenced in cancer cells via modulation of DNA methylation [307]. Both sulforaphane and 3,3'-diindolylmethane were shown to decrease DNA methyltransferase expression leading to a genome-wide promoter hypomethylation in human androgen-dependent and independent prostate cancer cells [307]. Intriguingly, sulforaphane and 3,3'-diindolylmethane shared similar gene targets, which are highly involved in cancer progression, within a single cell line [307]. Phenethyl isothiocyanate was found to suppress growth and induce apoptosis in cancer cells [308]. Human prostate cancer LNCaP cells exposed to phenethyl isothiocyanate exhibited demethylation of the *GSTP1* gene promoter, decreased HDAC activity, and activated histone acetylation and methylation on specific genes [309].

Epigenetic activity of retinoic acid is mediated by its interaction with their nuclear receptors RAR -α, -β and -γ subsequently leading to modulation of target gene promoters, including *CDKN1A* and *AP-1* [310, 311]. For example, retinoid acid activated the *CDKN1A* expression in human cervical squamous carcinoma, and inhibited AP-1 transcriptional activity in human gastric cancer cells [312, 313]. To uncover the molecular mechanism underlying these events, DNMT1 was shown to form protein-protein complexes with Proliferating Cell Nuclear Antigen (PCNA) and Ubiquitin-like, containing PHD and RING Finger domains-1 (UHRF1) proteins [314-318]. Furthermore, the disruption of DNMT1/PCNA/UHRF1 interactions modulates the DNMT1 activity and promotes a global DNA hypomethylation in human gliomas [316, 317, 319]. As shown, CDKN1A binds to PCNA, while the latter associates with DNMT, however, the phosphorylation of the former at the Serine-146 inhibits this protein-protein interaction [320, 321]. Emerging evidence suggests that cell cycle regulator CDKN1A may regulate methylation by blocking access of DNMT to PCNA [314, 320, 321].

AP-1 induces the *DNMT1* gene expression via binding to the specific *DNMT1* regulatory region [322]. Inhibiton of AP-1 activity by retinoid acid was shown to downregulate AP-1 responsive genes (e.g. *DNMT1),* and thus decrease global DNA methylation [313]. Modulation of DNA methylation patterns by retinoic acid can contribute to its anti-proliferative, and pro-apoptotic actions observed in leukemia, breast, prostate, pancreatic, and head and neck cancers [323-331]. Treatment of human MCF-7 breast cancer cells with retinoid acid reduced promoter methylation and increased in the expression of *RARβ2* and *PTEN* tumor suppressor genes, as well as inhibited breast cancer growth [84, 186, 332, 333]. Genome-wide analysis of the potential effects of all-trans retinoid acids on gene methylation and ex-

pression in neuroblastoma revealed that retinoic acid compounds reduced the expression of methyltransferases, DNMT1 and DNMT3B, while induced the expression of microRNAs targeting these DNMT proteins [334, 335].

Cucurbitacin B, a single bioactive triterpenoid natural compound, was shown to inhibit DNMTs and HDACs in H1299 non-small cell lung cancer cells leading to the reactivation of tumor suppressor genes (e.g. *CDKN1A* and *CDKN2A*), as well as downregulation of oncogenes (e.g. *c-MYC* and *K-RAS*), and human *TERT* gene [336]. Cucurbitacin B markedly decreased growth of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumors in A/J mice [336]. Z-Ligustilide from *Radix Angelicae Sinensis* was shown to restore *Nrf2* gene expression in mouse TRAMP C1 cells through epigenetic modification leading to an increase expression of endogenous *Nrf2* mRNA and Nrf2 protein, as well as *Nrf2* downstream target genes (e.g. *Ho1*, *Nqo1,* and *Ugt1a1*), as reviewed elsewhere [337]. Z-Ligustilide treatment decreased the level of methylation of the *Nrf2* promoter region, binding of anti-methyl antibody to the *Nrf2* promoter, as well as inhibited DNMT activity *in vitro* [337]. This study demonstrated that the expression of *Nrf2* is likely to be controlled by epigenetic alterations, since these changes were reversed by natural compounds resulting in the prevention of carcinogenesis in the mouse TRAMP prostate cancer model [337].

Kazinol Q, a natural compound from *Broussonetia kazinoki*, was shown a promise as an inhibitor of DNMT1 [338]. Kazinol Q inhibited DNMT activity and subsequently reactivated the expression of a DNA methylation-silenced gene, *CDH1* encoding E-cadherin, in MDA-MB-231 breast cancer cells [338]. Furthermore, kazinol Q inhibited the proliferation of human breast cancer MCF-7 cells and prostate cancer LNCaP cells via induction of apoptosis [338]. Similarly to EGCG, kazinol Q inhibited DNMT activity by competing with cytosine binding [338]. An aqueous extract of *Opuntia ficus indica*, and its bioactive ingredient, betalain indicaxanthin, was reported to upregulate demethylation of the tumor suppressor gene CDKN2A [339]. *Annurca* apple from southern Italy is rich in polyphenols that are associated with anticancer properties showing their ability to induce cell death in colorectal cancer cell lines (RKO, SW48, and SW480), as reviewed in [340]. Treatment of tumor cells with the *Annurca* apple extract led to a significant increase of TP53 protein expression, as well as to a reduced promoter DNA methylation for *MLH1*, *ARF1*, and *CDKN2A* genes due to a marked downregulation of DNMT protein levels [340]. Modulating effects of polyphenols, caffeic acid and chlorogenic acid, were reported on methylation of the *RARβ* promoter DNA region in MCF-7 and MAD-MB-231 human breast cancer cells [341]. Phenolic natural compounds, bromotyrosines, accumulated by marine sponges (e.g. *Aplysinella rhax, Suberea mollis, Verongia aerophoba, Lanthella basta* order *Verongida,* family *Aplysinidae*) include: psammaplin A, aerothionin, aeroplysinin-1, dienone, and bastadins) were shown to exhibit modulating activities towards epigenetic targets, such as HDAC and DNMT [342].

Parthenolide, a sesquiterpene lactone from *Tanacetum parthenium*, was shown to exhibit anti-cancer properties by inhibiting NF-kB activation, but promoting ubiquitination of MDM2 and activating TP53 cellular functions [343-349]. Parthenolide decreases DNMT1 expression and activity in human leukemia cell lines (K562, Kasumi-1, MV4-11) and human MCF-7 breast cancer cells leading to a decreased global methylation and hypomethylation and activation of the Secretoglobin family 3A member 1 (*SCGB3A1*, also known as *HIN1*) tumor suppressor gene [350]. Fungal metabolite, verticillin A (*Verticillium* species-infected mushrooms), mediates its anticancer activity and overcomes apoptosis resistance in human colon carcinoma cells by inhibiting DNA methylation or inducing DNA demethylation of *BNIP3* gene encoding BCL2/adenovirus E1B 19 kDa protein-interacting protein involved in the regulation of apoptosis [351].

Folate, cobalamin, riboflavin, pirydoxine or methionine are involved in the regulation of the DNA methylation by controlling the level of a methyl donor, SAM [352-354]. Folate deficiency has been shown to increase DNMT1, DNMT3B, MBD2 and MBD4 levels in human hepatoma cells [355, 356]. The increase in DNMTs led to hypermethylation, whereas induced MBD2 and MBD4 levels underlie hypomethylation of oncogenes and metastatic genes [33, 223, 357]. The increasing concentrations of folic acid lead to a dose-dependent down-regulation of *PTEN*, *APC* and *RARβ2* tumor suppressor genes in MCF-7 and MDA-MB-231 breast cancer cell lines with different invasive capacity [358].

CHROMATIN PROTEIN MODIFICATIONS AND NATURAL COMPOUNDS

The histone modifications affecting chromatin architecture play important roles in the regulation of gene expression, as well as in initiation and progression of tumorigenesis [4, 17, 30, 31, 359]. Chromatin proteins are critically involved in the packaging of genomic DNA into nucleosome and higher order chromatin fibers. Histones maintain the stability of nucleosomes and the highly folded chromatin structures, as reviewed in [360]. Histone PTMs regulate the chromatin folding and packaging leading to the regulation of activation or repression of target genes, as reviewed in [360-366]. Each nucleosome consists of ~147 base pairs of DNA sequence wrapped around an octamer of histone proteins (e.g. double subunits of H2A, H2B, H3 and H4 core histones), as reviewed elsewhere [360-366]. Histone proteins are regulators of chromatin dynamics caused by specific PTMs (known as ”histone code’) or altering electrostatic charge [367, 368].

There are two types of chromatin entities: heterochromatin containing transcriptionally inactive genes) and euchromatin (containing transcriptionally active genes), as reviewed in [360-364]. On the one hand, heterochromatin is a tightly packed structure with almost no accessibility for transcription factors and RNA polymerase complex [360-364]. On the other hand, euchromatin is loosely packed and readily accessible to transcriptional factors and RNA polymerase to initiate and maintain gene transcription [360-364]. The majority of PTMs (e.g. acetylation, methylation, phosphorylation, ubiquitination, and sumoylation) occur at the lysine, arginine, and serine residues of the N-terminal histone tails extending from the histone core [361]. These modifications

of histone proteins could activate or repress the transcription of the target genes, depending on the location and the type of the PTMs involved [361].

A number of histone-modifying enzymes are involved in histone modifications, as reviewed elsewhere [359-361]. Histone AcetylTransferases (HATs) and histone methyltransferases add acetyl groups and methyl groups, respectively, to the histone tails covalently. HDACs and histone demethylases, however, remove acetyl and methyl groups, respectively, from histones [361]. HATs have been divided into multiple classes—GNAT (GCN5, PCAF, HAT1, HPA2, HPA3, ATF-2, and NUT1), MYST (MOZ, YBF2, SAS2, and TIP60), EP300/CBP, SRC, CLOCK, RTT109 and TAFII250 (TAFII250) - based on structure, homology, and histone specificity [93, 369]. HATs catalyze histone acetylation, while assisting transcription factors to bind nucleosomal DNA on lysine residues in the N-terminal tails of core histones [93, 369]. On the contrary, HDACs catalyze deacetylation by cleavage of acetyl groups from the histone molecules, leading to a chromatin compaction and subsequently restricting the binding of transcription factors to DNA, thereby repressing gene expression [359, 369, 370]. To date, 18 HDACs and 25 HATs proteins have been identified. HDACs are divided into four classes—I, II, III and IV—based on homology, size, sub-cellular expression, and number of enzymatic domains, as reviewed in [370]. Class I HDACs (HDAC1, 2, 3 and 8) share sequence similarity with the yeast RPD3 deacetylase, and are localized mainly in the nucleus [370]. Class II HDACs (HDAC4, 5, 6, 7, 9 and 10) are homologous to the yeast Hda1 deacetylase, are nuclear and cytoplasmic. Class II HDACs are further subdivided into class IIa (HDAC4, 5, 7 and 9) and class IIb (HDAC6 and 10), as described elsewhere [370]. Class III HDACs are represented by sirtuins (SIRT1 to SIRT7), a family of seven HDACs sharing homology with yeast silent information regulator 2 (Sir2) [369]. Class IV has only one member, HDAC11 [371, 372].

TP53 is a key substrate for HDAC1; E3 ubiquitin-protein ligase MDM2 (Mouse Double Minute 2 homolog) recruits HDAC1, which subsequently induces the deacetylation of TP53 protein, in turn leading to a proteasome-dependent degradation of TP53, as reviewed in [370]. HDAC1 decreases DNA damage-induced TP53 acetylation, and inhibits the induction of CDKN1A (p21) and MDM2 [373, 374]. Both HDAC1 and HDAC2 recruited to DNA damage sites were shown to regulate the deacetylation of histones H3K56 and H4K16 suggesting their roles in transcription repression [370]. By association with the co-repressors SMRT and N-CoR, HDAC3 regulates the transcription of numerous gene targets [375]. HDAC4, HDAC6, HDAC9 and HDAC10 were reported to be involved in genome instability, transcription factor binding, and DNA repair, as reviewed in [376-378]. SIRT1, SIRT3 and SIRT6 play critical roles in genome stability and repair, gene transcription, cellular metabolism, stress response, and tumorigenesis, as reviewed in [370]. Several transcriptional factors (TP53, forkhead box transcription factor [FOXO]), and chromatin accessory proteins (non-homologous end joining factor, X-ray repair complementing defective repair protein Ku70, histone acetyltransferase KAT5 (TIP60), MRN repair complex consisting of double-strand break repair protein MRE11, DNA repair protein RAD50 and NBS1 [nibrin]) are inactivated by SIRT1 via deacetylation, as reviewed elsewhere [371]. SIRT3 has been shown to deacetylate and activate mitochondrial isocitrate dehydrogenase 2 leading to increased NADPH levels [370].

Deregulation of histone acetylation often occurs during tumorigenesis [29]. The tightly packed chromatin DNA associated with transcriptionally repressed genes associated with DNA hypermethylation catalyzed by DNMT, as well as with histone deacetylation catalyzed by HDAC [29, 370, 378]. However, acetylation of histones by HAT enzymes and DNA demethylation increased accessibility for transcription factors and their co-activator complexes leading to activation of gene transcription, as reviewed elsewhere [379-382]. In cancer cells, the balance between HAT and HDAC activities is disrupted, and often associated with higher levels of HDAC proteins, therefore tumor cells exhibit aberrant histone and non-histone protein acetylation patterns and epigenetic silencing of tumor suppressor genes, as reviewed in [382]. HDAC activity was reported to increase in metastatic prostate cancer cells compared with prostate hyperplasia, as reviewed in [382]. Intriguingly, HDAC inhibitors (e.g. suberoylanilide hydroxamic acid, valproic acid, depsipeptide, and sodium butyrate) are effective chemotherapeutic tools against prostate cancer cells *in vitro* and xenograft models *in vivo* [382].

Epigenetic effect of a given histone methylation mark is dependent on the modification site, as well as on the degree and symmetry of methylation [380-384]. Histone methylation serves as a docking site for effector proteins, such as methyl-lysine (e.g. TP53-binding protein 1, Jumonji domain containing 2A protein, and AT rich interactive domain 4A protein), or methyl-arginine binding domain-containing proteins (Survival motor neuron protein, Tudor domain-containing protein 3, Piwi-like protein 1, and Splicing factor 30), or chromodomain-containing proteins (e.g. chromodomain-helicase-DNA-binding proteins, CHD1-8 and heterochromatin protein 1, HP1), as reviewed in [216, 380-384]. Histone methylation occurs on either arginine or lysine residues. Lysine residues can be mono-, di-, or trimethylated by various histone methylation transferases from the SET domain protein family [367, 384-386]. Lysine methylation is not limited to histone proteins, as several non-histone proteins are also subject to methylation [367, 387]. Protein arginines can be mono- or di-methylated by the family of Protein aRginine MethylTransferases (PRMT) resulting in transcriptional activation of gene expression [367, 385-388]. There are nine PRMT proteins, which catalyze three types of arginine methylation - monomethylation and two types of dimethylation [367]. Protein arginine methylation was reported to regulate signal transduction, gene transcription, DNA repair and mRNA splicing [366].

Depending on the affected residue and number of added methyl groups, histone lysine methylation could result in either transcriptional activation or repression [367, 369]. Acetylation of histone H3K9ac leads to transcriptional activation, whereas, methylation of histones H3K9me, H3K9me2, and H3K9me3 could repress gene expression [369]. Depending on the balance between histone H3K9 acetylation and methylation, however, methylation of histone

H3K9me3 can activate gene expression [369]. Inactive gene promoter regions are enriched with histone H3 trimethylated at lysine 27 (H3K27me3) or at lysine 9 (H3K9me3), while active gene promoter regions contain histone H3 trimethylated at lysine 4 (H3K4me3). Regulatory enhancer sequences attached to histone H3 monomethylated at lysine 4 (H3K4me1) and acetylated at lysine 27 (H3K27ac), as described elsewhere [367, 369, 389]. The histone proteins coordinate the changing dynamics and reversible turnover between heterochromatin and euchromatin DNA in order to rapidly regulate gene transcription [367, 369, 385, 389-391]. For instance, euchromatin-specific PTMs (e.g. acetylation of histones H3 and H4, or di- or trimethylation (me) of histone H3K4) are associated with transcriptionalluy active genes, whereas di- or trimethylation of histone H3K9 and trimethylation of histone H3K27 are connected to repressed genes [367, 369, 385, 389-391]. Upregulation of the histone methyltransferase Enhancer of Zeste Homolog (EZH)-2 adds the trimethyl residues to histone H3K27 at the position Lysine-27, inhibits tumor suppressor gene expression, and increases tumor progression in human prostate cancer cells *in vitro* and *in vivo* [392-396].

Recently found several histone demethylases play important roles in demethylating lysines and regulation of gene transcription [392, 393]. For example, the upregulated levels of Lysine-Specific Demethylase (LSD1) are associated with an increase in tumor cell proliferation, aggressiveness in hormone refractory prostate cancer [397-399]. LSD1 was found to remove mono- or di-methyl groups from histone H3K4 leading to gene repression, since H3K4 methylation is an activating mark. In contrast, LSD1 demethylation of histone H3K9 leads to gene activation during epithelial-to-mesenchymal transition in the prostate cancer [398, 399].

A large number of natural compounds were shown affecting various histone-modifying enzymes [83, 100, 370, 378]. For example, resveratrol was found to downregulate expression of the MeTastasis Associated protein-1 (MTA1, a known component of the nucleosome remodeling and deacetylating complex [NuRD]), which is overexpressed in several cancers, including prostate cancer, as indicated elsewhere [58, 400, 401]. By downregulating MTA1 expression resveratrol disrupted the MTA1/HDAC interaction in NuRD co-repressor complex causing increased expression and acetylation of TP53, and subsequently leading to increased BAX and CDKN1A (p21) expression and apoptosis in prostate cancer cells [58, 400, 401]. While MTA1 was found to inactivate PTEN in prostate cancer cells, resveratrol promotes acetylation and reactivation of PTEN via inhibition of the MTA1/ HDAC complex, subsequently resulting in inhibition of the AKT pathway, as indicated in [58, 400, 401]. Resveratrol was also shown to re-activate TP53 acetylation in prostate cancer cells [58, 400, 401]. Pterostilbene, a natural resveratrol derivative found in blueberries, strongly increased the MTA1-mediated acetylation of TP53, as described in [402]. Furthermore, resveratrol and pterostilbene significantly inhibited tumor growth, progression, local invasion and spontaneous metastasis in orthotopic prostate cancer xenografts, as shown in [402].

Resveratrol inhibited HDAC1, HDAC2, MTA1, MTA2 and MTA3 proteins of NuRD complex in DU145 prostate cancer cells and reactivated PTEN tumor suppressor by increasing its acetylation resulting in inhibition of AKT survival pathway in prostate cancer [58, 400]. Resveratrol was shown to induce autophagy by activating the NAD-dependent deacetylase, SIRTuin (SIRT)-1, as reviewed in [93]. However, other phenolic compounds found in red wine, including anthocyanins (oenin), stilbenoids (piceatannol), monophenols (caffeic acid, gallic acid) glucosides (delphinidin, kuronamin, peonidin) and flavonoids (catechin, epicatechin, quercetin, myricetin), were found to promote autophagy, and protein deacetylation [403]. Resveratrol targets the class III HDAC, such as SIRT1, SIRT2, SIRT3, as well as HAT, EP300 [403]. Resveratrol was shown to regulate cell death process of prostate cancer cells *in vitro* by global modulation of gene expression through deacetylation of FOXO transcription factor in human pancreatic and prostate cancer cells *in vitro* and *in vivo* [404-406].

The hydroxamic acid trichostatin A from the actinomycete *Streptomyces hygroscopicus* is a potent pan-HDAC inhibitor and was found to induce apoptosis through increase in BAX and CASP3 protein levels and decrease in telomerase (TERT) expression [407]. The depsipeptide FK228 (or Romidepsin) from *Chromobacterium violaceum* found to specifically target class I HDACs, inhibited tumor cell growth via apoptosis in human leukemic cells [408, 409]. Moreover, FK228 induced the autophagy pathway associated with the Apoptosis Inducible Factor, AIF) translocation from mitochondria to the nucleus [410]. The FDA approved this compound, under a trade name Istodax, for the treatment of cutaneous T-cell lymphoma, as reviewed in [93]. Ursodeoxycholic acid (Ursodiol) from metabolic bycompounds of intestinal bacteria was found to modulate histone acetylation and induce senescence and recently shown acting as a potential anticancer drug for colon cancer prevention [93, 411].

A variety of natural compounds have been identified as inhibitors of histone acetyltransferases/ deacetylases, and histone methyltransferases/demethylases, as reviewed in [93]. Furthermore, many following natural compounds from plants, fungi and marine organisms could potentially modulate epigenetic enzymes involved in histone modifications [93]. Curcumin has been shown to alter stability of certain HAT proteins through a proteasome-dependent degradation of EP300 and CBP proteins without affecting histone acetyl transferase 2B (KAT2B or PCAF) and GCN5, as reviewed in [93, 412]. Curcumin effectively blocks histone hyperacetylation induced by the HDAC inhibitor MS-275 in prostate cancer PC3-M cells [412]. Inhibition of EP300/CBP activity by curcumin suppresses acetylation of histone and TP53 proteins [273, 413]. Human hepatoma cells treated with to curcumin exhibited a dramatic decrease in HAT activity [88]. The expression of HDAC1, HDAC3, and HDAC8 proteins was decreased, while the acetylated histone H4 level was increased in Raji cells upon curcumin exposure [414]. Human medulloblastoma cells (DAOY, D283 Med, and D341) exposed to curcumin, exhibit induction of cell cycle arrest and apoptosis, and reduced HDAC4 expression, increased tubulin acetylation, which eventually caused a mitotic catastrophe [415]. Curcumin also reduced growth of medulloblastoma xenografts tumors in *Smo/Smo* transgenic medulloblastoma mouse model, significantly increasing mouse survival [416]. Curcumin was also reported to induce downregulation

of EZH2 through activation of MAPK, JNK, ERK, and p38 MAPK, leading to anti-proliferative effects in human breast cancer cells [416].

Polyphenols abundant in vegetables, fruits, cereals, wine and tea were found to induce the SIRT1 deacetylase activity [417, 418]. EGCG, epicatechin galate and myricetin increased endogenous SIRT1 level, while quercetin was found to activate a recombinant SIRT1 activity [417, 418]. Quercetin was found to block a proliferation of colon cancer RKO cells *in vitro* by inhibit DNMT1 activity leading to a reverse in the hypermethylation of CDKN2A (p16INK4a) gene promoter DNA [419]. Quercetin has been shown to inhibit the EP300/CBP activity and phosphorylation/ acetylation of histone H3 [420]. EGCG decreased HDAC activity leading to elevated levels of histone H3-Lys 9 and H3-Lys14 and histone H4-Lys5, H4-Lys12, and H4-Lys16, but decreased levels of methylated histone H3-Lys 9 [421]. EGCG triggered upregulation of the RAF kinase inhibitor by inhibiting HDAC activity, which further increased the H3 histone expression [421].

EGCG reactivated the Tissue Inhibitor of matrix MetalloProteinase-3 (*TIMP3*) gene expression in human MCF-7 and MDA-MB-231 breast cancer cells [422]. The polyphenols (e.g. EGCG) further reduced EZH2 and class I HDAC levels. Studies showed the EGCG-mediated decrease in EZH2 and histone H3K27, and increase in H3K9/18 acetylation at the TIMP-3 promoter [422]. Green tea polyphenols induced TP53-dependent downstream targets CDKN1A and BAX in human prostate cancer LNCaPshV cells [422]. These compounds also inhibited class I HDAC protein level, while induced acetylated histone H3 level associated with chromatin subsequently activation of the CDKN1A and BAX gene promoter activities [423-425]. The polycomb group proteins enhance cell survival by epigenetically regulating gene expression [426]. Increased levels and enhanced activity of polycomb complex proteins lead to increased methylation and reduced acetylation of the histones associated with tumor suppressor genes, causing reduced tumor suppressor activity and increased cell proliferation and survival [426]. Increased expression of key polycomb proteins, BMI1 and EZH2, was found in both immortalized keratinocytes and skin cancer cell lines [427]. EGCG treatment of SCC-13 skin cancer cells reduced BMI1 and EZH2 protein levels, and global reduction in histone H3K27 trimethylation [427].

Isoflavones, genistein, and daidzein, were shown to increase estrogen receptor-mediated core histone acetylation through inducing the activities of HAT and steroid receptor co-activator 2 (SRC2), as indicated in [428]. Genistein activated the *CDKN1A and CDKN2A* gene expression in human prostate cancer cells through upregulation of the HAT expression, while blocked HDAC6 [429, 430]. Genistein also promoted demethylation and acetylation of histone H3-K9 at the *PTEN* and *CYLD* promoters, as well as induced acetylation of histone H3K9 on the *TP53* and *FOXO3A* gene promoters through reduction of SIRT1 activity [431]. Subsequently, the genistein-induced expression of tumor suppressor genes, TP53 and FOXO3 led to an inhibition of the AKT signaling pathway [431]. Genistein was also reported to induce expression of the DicKKopf-related protein-1 (*DKK1*) gene by acetylation of histone H3 at the DKK1 promoter region in colorectal adenocarcinoma cells (HCT15 and SW480), as described [432]. Genistein activated phosphorylated TP53 and ATM levels, leading to CDKN1A induction and histone γH2AX formation [433].

Epigenetic effects of many isothiocyanates from cruciferous plants (*Brassicaceae*) have been linked to the inhibition of HDAC activity and histone hyperacetylation [300, 434]. In addition, isothiocyanates could alter histone methylation modifications [434, 435]. Sulphorafane decreased the HDAC3 and HDAC6 protein expression in HCT116 colon cancer cells, leading to acetylation of histone H4 and tubulin, respectively [435]. Since HDAC3 is a key component for maintaining chromatin structure and undergo DNA repair, the potential ability for sulphorafane to affect HDAC3 is critical for chromatin integrity, mitotic spindle assembly, and DNA replication [374]. In APCMin/+ mouse model, the sulforaphane treatment reduced a cancer formation (by 40%) and increased global histone acetylation and increased association of acetylated histone H3 on the *CDKN1A* and *BAX* gene promoters leading to an increased expression of these genes [436, 437]. Sulforaphane reduced the polycomb group protein (BMI1, EZH2) expression in SCC-13 skin cancer cells and decreased histone H3K27 level through a proteasome-dependent degradation [438]. Human prostate cancer LNCaP cells exposed to phenethyl isothiocyanate exhibited also decreased the activity of HDACs, while inducing a specific histone acetylation and methylation [439].

Cruciferous vegetables also contain glucoraphanin (the precursor of sulphorafane), and glucobrassicin (the precursor of indole-3-carbinol), and its acid condensation compound, 3,3'-diindolylmethane [440]. Indole-3-carbinol increased ATM-dependent TP53 phosphorylation leading to CDKN1A expression and cell cycle arrest at the G1 phase in human breast cancer cells [440]. Diindolylmethane was shown to selectively induce a proteasomal degradation of HDAC1, HDAC2, HDAC3, and HDAC8 proteins without affecting class II HDAC proteins in human colon cancer cells *in vitro* and *in vivo* [441]. The alterations in HDAC1, HDAC2, and HDAC3 levels led to an increased expression of CDKN1A (p21) and CDKN1B (p27) genes and subsequently to cell cycle arrest and DNA damage in cancer cells [441]. Diindolylmethane caused a significant increase in γH2AX level and phosphorylation of tripartite motif-containing-28 protein (also known as transcriptional intermediary factor 1β, or KRAB-associated protein-1) prior to DNA damage-triggered apoptosis [87, 441].

Organosulfur compounds from *Allium sativum* (such as diallyl sulfide, diallyl disulfide and diallyl trisulfide) inhibited growth of cancer cells by causing cell cycle arrest and apoptosis, inhibits angiogenesis and suppresses metastasis [442, 443]. Treatment of DS19 mouse erythroleukemia cells with allyl isothiocyanate (from black mustard *Brassica nigra* or brown Indian mustard *Brassica juncea*) increased the histone acetylation [444]. Diallyl disulfide and S-allylmercaptocysteine were found to induce histone acetylation and inhibited growth in mouse erythroleukemia DS19 cells [444, 445]. Diallyl disulfide caused an increased global acetylation of histones H3 and H4 leading to upregulated binding of acetylated histone H3 to the *CDKN1A* gene pro-

moter, subsequently leading to an increase in the *CDKN1A* expression, cell cycle arrest and HDAC inhibition [446, 447]. S-allylmercaptocysteine and diallyl disulfide induced acetylation of histone H3K14 in human colon cancer cells (Caco-2 and HT-29) and human breast cancer T47D cells [446-448].

Parthenolide, a sesquiterpene lactone from *Tanacetum parthenium*, was found to induce cell cycle arrest, and apoptosis, as well as downregulate HDAC1 level via a proteasome-dependent degradation [449-451]. Psammaplin A, a natural compound isolated from marine sponges, exhibits anticancer activity against several human cancer cell lines [213, 452-455]. As a natural prodrug that inhibits class I histone deacetylase, Psammaplin A decreased SIRT1 protein level and activity, as well as acetylation of TP53 in doxorubicin-resistant MCF-7/adr human breast cancer cells [454, 455]. The anacardic acid (6-pentadecyl salicylic acid from cashew nut shell liquid) was found acting as a potent inhibitor of EP300 and CBP-associated HAT activities [87, 456]. The cyclic tetrapeptide 1-alaninechlamydocin from a fungi *Tolypocladium sp*. showed the tumor-inhibitory effects on pancreatic cancer MIA PaCa-2 cells of via inhibition of HDAC activity [457].

Triptolide from *Tripterygium wilfordii Hook F* was found to induce apoptosis in human multiple myeloma cells through downregulation of c-MYC and vascular endothelial growth factor A (VEGFA) expression by blocking the accumulation of histone H3K4me3 on their promoters, as described elsewhere [458, 459]. Treatment with triptolide (minnelide) or siRNA-mediated silencing of Heat Shock Factor-1 (*HSF1*) gene expression disrupts the cytosolic complex between HSF1 protein, transitional endoplasmic reticulum ATPase (TER ATPase, also known as valosin-containing protein, or p97), heat shock protein (HSP)-90 and HDAC6, as indicated in [460]. Triptolide suppressed growth of human prostate cancer PC-3 cells and reduced the EZH2 expression, as described in [461]. PC-3 cells exposed to triptolide further exhibited upregulation in the ADRB2, CDH1, CDKN2A and DAB2IP expression modulated by EZH2 [461]. Triptolide suppressed the proliferation of multiple myeloma cells by inducing cell cycle arrest in G0/G1 phase and apoptosis [462]. Triptolide suppressed the expression of dimethylated histone H3K4, dimethylated histone H3K9 and dimethylated histone H3K36 by altering the expression of histone demethylases LSD1 and JMJD2B [462]. Triptolide blocked TNF-induced ubiquitination, phosphorylation, and degradation of IκBα, the inhibitor of NF-κB and inhibited acetylation of p65 subunit of NF-κB through suppression of binding of p65 to CBP/p300, as indicated in [463]. Triptolide also inhibited the IκBα kinase (IKK) that activates NF-κB and phosphorylation of p65 at the positions S276 and S536, as described in [463]. Furthermore, the NF-κB reporter activity induced by TNF-TNFR1-TRADD-TRAF2-NIK-TAK1-IKKβ was blocked by triptolide [463]. Triptolide also inhibited the TNF-induced expression of XIAP, BCL-xL, BCL-2, survivin, cIAP-1 and cIAP-2, as well as CCND1, c-MYC and COX-2, and metastasis proteins (e.g. ICAM-1 and MMP-9), as described in [463].

Selenoproteins and organoselenium metabolites as accumulated forms of selenium found in Brazil nuts and seafood were shown to exhibit inhibitory effects on cancer cells [464]. Some forms of organoselenium metabolites (e.g. sodium selenite, keto-methylselenobutyrate, methyl selenocysteine, and methyl selenopyruvate) were found to modulate gene expression through inducing histone PTMs. For example, they were shown to decrease of HDAC activity and increase of histone acetylation, and phosphorylation [465, 466]. Selenomethionine was observed to induce the specific phosphorylation of histones located at the DNA promoter sequence of *GJB2* (connexin 26) and *SKG1* (serum glucocorticoid kinase-1) genes [467].

Sinapinic acid extracted from *Hydnophytum formicarum Jack* rhizome was shown to inhibit HDAC activity, thereby blocking proliferation of several human cancer cell lines [468]. The epipolythiodioxopiperazine fungal metabolite, Chaetocin from *Chaetomium minutum,* is found to specifically inhibit the human histone-lysine N-methyltransferase SUV39H1, a human homolog of Drosophila SU (VAR) 3-9 protein [469]. Verticillin A from *Verticillium* sp. is a promising selective inhibitor of histone methyltransferases SUV39H1, SUV39H2, and G9a/GLP decreased H3K9me3 levels in the FAS promoter and restored FAS expression thereby inhibiting in colon carcinoma growth *in vivo*, as described elsewhere [470].

SHORT NON-CODING MICRORNAS AND NATURAL COMPOUNDS

The short non-coding RNAs, namely microRNA (miRNA), play special roles in epigenetic regulation of gene expression at the post-transcriptional and post-translational levels, as reviewed elsewhere [471, 472]. These short microRNAs (17-25 base pairs in length) often inhibit translation and/or induce degradation of their target mRNAs, thereby ultimately decrease the expression of certain genes [472]. Similarly to mRNA production, microRNAs are transcribed RNA polymerases II and III; however, they are encoded by the exons and introns of non-coding genes, as well as by the introns of protein-coding genes [473]. MicroRNAs are sequentially processed from longer precursor molecules into mature microRNA molecules, as reviewed in [473]. Primary microRNA transcripts (pri-microRNAs) are processed in the nucleus by the RNA-Induced Silencing Complex (RISC) to generate mature microRNAs [474, 475]. The pri-microRNAs contain one or more ~ 7 base pairs stem-loop structures. The ribonuclease DROSHA removes the stem-loop structures to form the precursor microRNAs (or pre-microRNAs) [474, 475]. Finally, the ribonuclease DICER processes pre-miRNA (exported from nuclei to the cytoplasm) into a short RNA duplex [474]. After untwisting, one RNA strand becomes the mature single-stranded microRNA, while the complementary strand is usually rapidly degraded [471-475].

Mature microRNAs form complementary duplexes with their mRNA targets based on specific sequences usually within the 3′-untranslated region (UTR) of the target mRNA [476]. Interestingly, one microRNA could potentially inhibit several mRNAs, while a few microRNAs were found to modulate the same mRNA target expression [476]. More than 1000 human microRNAs have been identified so far, which enable them regulate a large percentage of genes,

however, the database of microRNAs and their potential target genes is growing rapidly [477]. MicroRNA-modulated changes in gene expression appear to be heritable, therefore contributing to epigenetic regulation of cellular functions [474, 477]. Aberrant microRNA regulation associated with cancer development can be influenced by DNA methylation and histone PTMs, however, various microRNAs could regulate the expression of multiple enzymes involved in the epigenetic molecular mechanisms [472, 477-480].

MicroRNAs were found to control a plethora of molecular and cellular functions, such as cell proliferation, apoptosis, cancer development, cell cycle, and immunity, as reviewed in [481, 482]. MicroRNA gene expression is altered in various human cancers, and specific microRNAs have shown the oncogenic, tumor-suppressive or apoptotic potential, as reviewed in [481, 482]. Several microRNAs were found to control epigenetic regulatory components involved in transcription, as well as affect cellular metabolism, cell death, cell cycle arrest, autophagy and senescence, and contribute to epithelial stem cell maturation, as reviewed in [481, 482]. Some microRNAs were recently shown to directly bind the promoter sequences and gene 3'-end sequences, and were able to modulate gene transcription [483-485]. On the other hand, tumor cells often exhibit deregulated transcription of specific microRNA genes, which links to tumorigenesis, and microRNA profiles are often used to test the appearance of human cancer cells [484, 485]. Modulatory effects of microRNA on the epigenetic machinery, as well as the reciprocal epigenetic control of microRNA genes suggests that their deregulation might have important implications for global regulation of epigenetics in cancer cells, as reviewed in [473, 478, 479]. Accumulating evidence shows that various natural compounds exhibited an ability to affect microRNA expression in cancer cells, thus making these compounds a new source of potential anticancer drug agents, which could contribute to a development of novel therapeutic approaches for cancer chemoprevention, as reviewed in [89, 486-489].

Cucumin deregulated the expression of 29 microRNAs in human pancreatic carcinoma BxPC-3 cells [490]. Curcumin-induced upregulation of miR-22 was further found to suppress the expression of its target genes *SP1* (specificity protein 1) and *ESR1* (estrogen receptor 1) transcription factors [490]. Curcumin was shown to promote apoptosis in A549/DDP multidrug-resistant human lung adenocarcinoma cells by decreasing the miR-186 level, which in turn led to upregulation of CASP-10 level [491]. Curcumin was reported to decrease BCL-2 expression in human breast cancer MCF-7 cells by inducing miR-15a and miR-16 levels [492]. Curcumin was found to suppress miR-21 levels that led to a decrease in invasiveness and metastatic capabilities of human colon cancer RKO and HCT116 cells [493]. The miR-21 gene promoter region contains a few binding sites for the AP-1 transcription factor, and curcumin reduces the binding of AP-1 to the miR-21 promoter, while inducing the expression of the tumor suppressive ProgrammeD Cell Death protein 4 (*PDCD4*), which is a known target for miR-21 [493]. Curcumin reduced the miR-21 and miR-34a levels (known to affect NOTCH1), and induced let-7a miRNA level in esophageal cancer cell lines [494]. Curcumin was recently reported to inhibit a growth of prostate carcinoma *in vivo* through decreasing the miR-208 level, and subsequently leading to CDKN1A upregulation [495]. In mouse xenograft model of colorectal cancer, both curcumin and 3 acetyl-11-keto-β-boswellic acid inhibited tumor growth, associated with alterations in the miR-34a and miR-27a levels, confirming previous observations with *in vitro* studies [496]. Curcumin exposure triggered the induction of the TP53-miR-192-5p/215-XIAP pathway and apoptosis in non-small cell lung cancer cells [497]. Curcumin-mediated induction of miR-9 that leads to a modulation of AKT/FOXO1 axis underlies the cytotoxic effect of the drug against SKOV3 ovarian cancer cells [498]. Curcumin was also shown affecting the miR-19/PTEN/ AKT/p53 axis and decreasing a bisphenol A-induced cell proliferation, as well as inducing miR-181b and preventing metastasis via down-regulation of the inflammatory cytokines CXCL-1 and -2 in breast cancer cells *in vitro* and *in vivo* [499, 500].

Resveratrol (trans-3, 4', 5-trihydroxystilbene) was found to variably increase the levels of 22 microRNA, and decrease the levels of 26 microRNAs in human SW480 colon cancer cells [501]. Several microRNAs downregulated by resveratrol were oncogenic microRNAs (e.g. miR-21, miR-25, and miR-92a-2) and are overexpressed in colorectal cancer [501]. However, the tumor suppressing miR-16-1 was also downregulated by resveratrol [501]. *In silico* analysis showed that resveratrol deregulated microRNAs could potentially target known tumor suppressor genes (MLH3, MSH2 and MSH3, PDCD4 and PTEN), as well as critical effectors of the TGFβ signaling pathway, and a regulator of microRNA processing, DICER1 [501]. Resveratrol inhibited glioma cell proliferation inducing cell cycle arrest and apoptosis *in vitro* [502, 503]. Resveratrol was reported to markedly downregulate miR-21, miR-30a-5p and miR-19, and altered the expression of their mRNA targets known to act as critical regulators for initiation and progression of gliomas (e.g. TP53, PTEN, EGFR, STAT3, COX2, NF-κB and members of PI3K/AKT/mTOR pathway), as described elsewhere [502, 503]. Resveratrol was also shown to inhibit the migration/invasion in human osteosarcomas *in vitro* and lung metastasis *in vivo* by suppressing Matrix MetalloProteinase-2 (*MMP2*) [504]. Resveratrol modulated the MMP2 transcription through reducing the ability for CREB protein to bind DNA specific elements [504]. Moreover, miR-328 was predominantly upregulated in human osteosarcoma cells after resveratrol treatment [504]. Silencing of miR-328 significantly reduced the suppressing effect of resveratrol on the MMP2 expression and cell motility, while the forced miR-328 expression decreased MMP2 expression and invasive abilities [504].

Resveratrol induced the cytotoxicity and apoptosis of human bladder cancer cells (T24 and 5637 cells) in a dose-dependent manner [505]. While inducing apoptosis resveratrol decreased the miR-21 level, and subsequently the phosphorylated AKT and BCL2 protein levels in human pancreatic cancer cells (PANC-1, CFPAC-1 and MIA Paca-2), as described in [505, 506]. Based on microRNA microarray studies, resveratrol was found to reduce the expression of various prostate-tumor associated microRNAs, including miR-21 in androgen-receptor negative and highly aggressive human prostate cancer cells (PC-3M-MM2), as described elsewhere [507]. Resveratrol was also shown to upregulate

the expression of PDCD4 and maspin (encoded by *SERPINB5* gene), which were known targets for miR-21 [507]. Twenty-three miRNAs were significantly downregulated and twenty-eight miRNAs were markedly upregulated in prostate cancer cells after resveratrol treatment [508]. Among downregulated miRNAs, miR-17-92 and miR-106ab clusters were oncogenic miRNAs, while the upregulated miRs included several tumor suppressors [508, 509]. miR-17, miR-20a, miR-20b, miR-106a and miR106b were shown to target PTEN expression [509]. Resveratrol and pterostilbene were shown to decrease the levels of endogenous and exogenously expressed miR-17, miR-20a and miR-106b, thereby upregulating their target PTEN [509]. Furthermore, pterostilbene rescued PTEN levels leading to reduced tumor growth *in vivo* through downregulation of miR-17-5p and miR-106a-5p expression in tumors and systemic circulation [509].

Resveratrol was found beneficial against dextran sodium sulfate-induced colitis-associated tumorigenesis in the Apc (Min/+) mice [510]. Treatment of mice bearing colitis tumors with resveratrol led to a decreased number and size of polyps, and inhibition of proliferation of intestinal mucosa epithelial cells compared with control mice [510]. Among 104 microRNAs, whose expression was altered in the intestinal tissue of resveratrol-treated mice, miRNA-101b and miRNA-455 were validated to increase their levels upon resveratrol treatment [510]. A combination of resveratrol and quercetin decreased miR-27a level leading to an increasing expression of zinc finger protein repressor ZBTB10 known to suppress SP activity [511]. Piceatannol, a naturally occurring analog of resveratrol from roots of *Picea abies*, was shown to induce apoptosis in colorectal cancer cells (HCT116 and HT29) through upregulation of miR-129 levels, and downregulation of BCL2 level, as indicated in [512]. Knockdown of miR-129 counteracted the negative effect of piceatannol on viability of HCT116 and HT29 cells [512]. Resveratrol, EGCG, and α-mangostin were shown to induce apoptosis and suppress the PI3K/AKT signaling pathway [513]. Additionally, α-mangostin also suppressed MAPK/ERK1/2 signaling in human colon cancer DLD-1 cells [513]. Interestingly, resveratrol increased the miR-34a expression level leading to a downregulation of target protein E2F3 and its downstream SIRT1 resulting in growth inhibition [513].

EGCG treatment upregulated thirteen microRNAs and downregulated forty-eight microRNAs in human hepatocellular carcinoma HepG2 cells [514]. The potential target proteins for the upregulated microRNAs were - RAS, BCL2, E2F, TGFBR2 and c-KIT, while for downregulated microRNAs were - PTEN, SMAD, MCL1, SLC16A1, TTK, PRPS1, ZNF513, and SNX19 [517]. While EGCG decreased the level of an anti-apoptotic BCL-2 protein, the transfection with miR-16 inhibitor counteracted this effect by inducing apoptosis [514]. EGCG was found to upregulate the transcription of miR-210, which led to a reduced cell proliferation and anchorage-independent growth *in vitro* and in tobacco carcinogen-induced lung tumors in A/J mice *in vivo* [515, 516]. EGCG and Polyphenon® E downregulated the expression levels of miR-25, miR-92, miR-141, and miR-200a (known to target TP53) in human multiple myeloma cells [517]. Polyphenon-60 from green tea significantly downregulated the expression of miR-21 and miR-27 in human breast cancer MCF-7 cells [518]. EGCG enhanced apoptotic-inducing effect of cisplatin on non-small cell lung cancer (NSCLC) A549 cells by downregulating miR-98-5p and miR-125a-3p levels and activation of TP53 protein [519]. Combination of N- (4-hydroxyphenyl) retinamide and (-)-EGCG dramatically reduced the levels of oncogenic miR-92, miR-93, and miR-106b, and increased expression of tumor suppressing miR-7-1, miR-34a, and miR-99a in human malignant neuroblastoma SK-N-BE2 and IMR-32 cells [520].

Isoflavonoids were shown modulating expression of target genes in human prostate cancer by microRNAs, as reviewed in [262, 263]. Genistein and daidzein were found deregulating expression profiles of several microRNAs in human PC-3, DU 145, and LNCaP prostate cancer cell lines [262, 263]. While miR-15b, -125a, -125b, -155, -208b, -211, -320, -376a, -411, -520g and -542-5p were downregulated, miR-15a and miR-548b were upregulated [96, 262, 263]. Although miR-145 is silenced by promoter methylation in prostate cancer, genistein in combination with decitabine, was able to re-express miR-145, as indicated [262, 263]. Genistein was reported to induce expression of miR-1296; the latter is known to be downregulated in human prostate cancer specimens [521]. Forced expression of miR-1296 mimic significantly reduced the MiniChromosome Maintenance-2 (*MCM2*) gene expression [521]. Genistein also downregulated miR-221/222 expression thereby upregulating Aplasia Ras Homolog member I (*ARHI*, Ras-related small G-protein) levels, suggesting the role of epigenetic regulation of ARHI expression in anticancer effects of genistein [522]. Genistein markedly reduced miR-151 expression in human prostate cancer PC-3 cells, thereby modulating the level of the miR-151 targets SRY-Related HMG-BOX Transcription Factor-17 (*SOX17*) and Aplysia RAS-Related Epididymis Secretory Sperm Binding Protein (*ARHGDIA*, Rho GDP Dissociation Inhibitor-alpha), as indicated in [523]. Treatment of human prostate cancer cells with a mixture of genistein, daidzein and glycitein led to a promoter demethylation and increased levels of miR-29a and miR-1256 [262, 263]. Genistein significantly decreased expression of oncogenic miR-1260b in renal and prostate cancer cell lines [524, 525]. Knockdown of miR-1260b decreased proliferation, invasion ability and increased apoptosis in PC-3 cells [524, 525]. Genistein treatment leads to upregulation of Secreted Frizzled-Related Protein (SFRP)-1 and SMAD family member 4 protein, which are reported to be targets of miR-1260b, thereby reducing the levels of H3K9me2, -me3 and H3K27me3 at the *SFRP1* and *SMAD4* gene promoters [525].

Genistein treatment was reported to significantly inhibit oncogenic miR-223 expression and upregulated the expression of the F-Box and WD repeat domain containing-7 (*FBW7*) E3 ubiquitin protein ligase, which is one of the miR-223 targets in pancreatic cancer cells [526]. Moreover, silencing of miR-223 reduced tumor cell growth and promoted apoptotic cell death in pancreatic cancer cells [526]. Genistein was found to induce the expression of miR-574-3p in human prostate cancer cells leading to inhibition of cell proliferation, migration and invasion *in vitro* and *in vivo* [527]. The miR-574-3p mimic induced apoptosis by modulating BCL-XL level and increasing the levels of activated

CASP3 and CASP9 proteins [527]. MiR-574-3p was shown to target the expression of several target genes (RAC1, EGFR and EP300) *in vitro* [528]. Genistein was found to inhibit the growth and migration of ovarian cancer cells, pancreatic cancer cells and uveal melanoma cells through a downregulation of miR-27a expression leading to an increased expression of the Sprouty homolog-2 protein (encoded by *SPRY2* gene), a receptor tyrosine kinase inhibitor and putative miR-27a target gene [529-531]. Genistein also inhibited expression of oncogenic miR-23b-3p and reactivation of its target PTEN in renal cell carcinoma cell lines [531].

Claudin-2 (*CLDN2*) expression is upregulated in human lung adenocarcinomas *in vitro* and *in vivo*, while silencing of its expression leads to reduced cell proliferation and migration of tumor cells suggesting that claudin-2 is a potential target for lung adenocarcinoma [532]. Quercetin increases the expression of miR-16 leading to downregulation of claudin-2 protein level, miR-16 inhibitor reverted this effect in lung adenocarcinoma A549 cells [532]. Upon quercetin exposure miR-34a level was upregulated in human hepatocellular carcinoma HepG2 cells (expressing wild-type TP53 protein) [533]. Downregulaiton of miR-34a led to resistance of tumor cells to quercetin exposure, while exhibiting the increased level of SIRT1, and decreased level of acetylated TP53 suggesting a TP53/miR-34a/SIRT1 signal feedback loop [533]. Quercetin in combination with cisplatin suppresses growth and invasiveness, as well as upregulates the expression of miR-217 leading to a downregulation of the miR-217 target KRAS in human osteosarcoma cells (143B) [534].

Triptolide, a diterpenoid epoxide from *Tripterygium wilfordii,* was reported to inhibit a pancreatic ductal adenocarcinoma cell growth *in vitro* and decrease metastasis *in vivo* [535]. Both triptolide and quercetin upregulate miR-142-3p in pancreatic ductal adenocarcinoma cells (MIA PaCa-2, Capan-1, and S2-013), as indicated in [535]. Ectopic expression of miR-142-3p inhibited cell proliferation, and decreased the expression of its target, heat shock protein-70 in tested pancreatic cancer cells *in vitro* [535]. Minnelide, a water-soluble prodrug of triptolide, induced the expression of miR-142-3p in non-small cell lung carcinoma and in a xenograft model of mesothelioma *in vivo* [536, 537]. Ellagitannins derived from pomegranate, raspberries, walnuts and almonds exhibit potent anticancer properties [538]. Ellagitannin BJA3121 from *Balanophora japonica* reduced a proliferation of in liver cancer cells and upregulated of miR-let-7e, miR-370, miR-373 and miR-526b levels, while downregulated of let-7a, let-7c, let-7d levels [539]. *Olea europaea* leaf extract induced anti-proliferative effects and altered the expression levels of miR-181b, miR-153, miR-145, miR-137, and let-7d in human glioblastoma T98G cells [540].

Honokiol (HNK) from *Magnolia grandiflora* was shown to reduce a tumor growth of leptin-induced breast cancer, its invasiveness and migration properties *in vivo* [541]. HNK was found to repress Wnt1-MTA1-β-catenin signaling *in vitro* and *in vivo* [544]. HNK decreased STAT3 phosphorylation, and inhibited its recruitment to the miR-34a promoter [541]. 3,3'-diindolylmethane upregulated let-7 microRNA level and downregulated EZH2 level in human prostate cancer cells [542]. Both 3,3'-diindolylmethane and genistein caused upregulation of let-7b, let-7e, miR-200b, and miR-200c in gemcitabine-resistant human pancreatic cancer cells [543]. The potential targets of these microRNAs were E-cadherin, an epithelial cell marker and mesenchymal markers, Zinc Finger E-Box Binding Homeobox 1 (*ZEB1*) and vimentin (*VIM*) suggesting that diindolylmethane could influence the invasion capacity of pancreatic cancer cells through a microRNAs [543]. Diindolylmethane upregulated miR-146 level, and reduced the levels of epidermal growth factor receptor (*EGFR*), MTA2 metastasis associated 1 family, member 2 (*MTA2*) and members of the NF-kB signaling pathway in pancreatic cancer cells [544].

CONCLUSION

"Over 60% of the currently used anti-cancer drugs come from the natural compounds derived from plants, fungi and marine organisms" [545]. Natural compounds with anticancer activities derived from various habitats have been shown to modulate multiple molecular targets affecting numerous "signaling and regulatory pathways ultimately leading to tumor cell death" [546, 547]. They affect numerous targets including transcriptional factors, epigenetic regulators, regulators of mammalian target of rapamycin pathway, intrinsic and extrinsic apoptosis, cell cycle regulators, ligand-dependent receptor activators, and oxidative stress modulators leading to cell cycle arrest, apoptosis, necroptosis, and autophagy [264, 542, 548]. Molecular mechanisms controlling cell cycle arrest, apoptosis, autophagy and necroptosis are closely related, so targeting these pathways simultaneously may help to induce the cell death of cancer cells and overcome the resistance of tumor cells to anticancer drugs [344-550].

"Currently, there are more than 200 naturally produced drugs already in preclinical/clinical development or in the clinic", as reviewed elsewhere [545, 546]. Promising anticancer agents were obtained from plants (vincristine, vinblastine, etoposide, paclitaxel, camptothecin, topotecan and irinotecan), marine organisms (citarabine, aplidine and dolastatin) and microorganisms (dactinomycin, bleomycin and doxorubicin). In addition, other natural compounds that can be used in anticancer therapy were purified from fruits and vegetables. They include: curcumin (turmeric), resveratrol (red grapes, peanuts and berries), genistein (soybean), diallyl sulfide (allium), S-allyl cysteine (allium), allicin (garlic), lycopene (tomato), capsaicin (red chilli), diosgenin (fenugreek), 6-gingerol (ginger), ellagic acid (pomegranate), ursolic acid (apple, pears, prunes), silymarin (milk thistle), anethol (anise, camphor, and fennel), catechins (green tea), eugenol (cloves), indole-3-carbinol (cruciferous vegetables), and limonene (citrus fruits), as reviewed elsewhere [545-549].

A number of studies have shown that specific natural compounds, such as curcumin, EGCG, resveratrol, sulforaphane, gallic acid, genistein and 3,3'-diindolylmethane altering epigenetic processes, including DNA methylation, histone modification, chromatin remodeling, microRNA regulation and targeting cancer stem cells [82, 83, 86, 87, 89-96, 133, 153, 213, 269, 272, 434, 442, 486-489, 550]. The (Table **1**) summarizes known natural compounds found to affect activity of numerous epigenetic enzymes. The

Table 1. Categorization of natural compounds affecting epigenetic functions in cancer cells.

Compound Name	Epigenetic Function	References
Curcumin	Induces TP63, MAX; inhibits NF-κB, OCT4, NANOG, SOX2, c-MYC, NOTCH1, c-JUN, c-FOS, STAT3, FOXO3A; inhibits HDAC1; inhibits DNMT1; reverses methylation of the *NRF2* promoter; decreases MECP2 binding to the *NEUROG1* promoter; alters stability of certain HAT proteins through a proteasome-dependent degradation of EP300 and CBP proteins; inhibits the expression of HDAC1, HDAC3, HDAC4, and HDAC8 proteins; downregulates EZH2 through activation of MAPK, JNK, ERK, and p38 MAPK; upregulates let-7a, miR-9, miR-15, miR-16, miR-22, miR-181b; downregulates miR-21, miR-27a, miR-34a, miR-186, miR-208; activates the p53-miR-192-5p/215-XIAP pathway; modulates miR-19/PTEN/AKT/p53 axis.	[92, 111-117, 125, 152-155, 292, 293-296, 404, 406-408, 482-492]
Resveratrol	Inhibits HIF1a, NANOG, SOX2, OCT4, c-MYC; targets the class III HDAC (SIRT1, SIRT2, SIRT3), as well as HAT (EP300); deacetylates FOXO transcription factor; enhances TP53 protein acetylation and inhibits MTA1/NuRD protein complex; inhibits HDAC1 and HDAC2; downregulates oncogenic miR17-92, miR-106a-363 and miR-106b-25 clusters, miR-19, miR-21, miR-25, miR-30a-5p, and miR-92a-2; upregulates miR-328.	[58, 92, 150, 151, 152-155, 402-404, 493-499, 501]
Epigallocatechin-3-gallate	Induces TP53, stimulates p38 MAPK and JNK; inhibits NF-κB, AP-1, ATF-2, CREB, and HIF1α, STAT3, NANOG, SOX2, OCT4, c-MYC; activates NRF2; inhibits DNMT and reactivates gene expression; reduces HDAC and DNMT expression; stimulates SIRT1 activity; decreased HDAC activity and increased levels of acetylated lysine 9 and 14 on histone H3 (H3-Lys 9 and 14) and acetylated lysine 5, 12 and 16 on histone H4 but decreased levels of methylated histone H3-Lys 9; reduces EZH2 and class I HDAC protein levels; reduces BMI1 and EZH2 protein levels, and histone H3K27 trimethylation; upregulates thirteen microRNAs and downregulates forty-eight microRNAs; the potential target proteins for the upregulated microRNAs were - RAS, BCL2, E2F, TGFBR2 and c-KIT, while for downregulated microRNAs were - PTEN, SMAD, MCL1, SLC16A1, TTK, PRPS1, ZNF513, and SNX19; upregulates miR-210, reduces the TP53-targeting microRNAs, including miR-25, miR-92, miR-141, and miR-200a; downregulates miR-98-5p and miR-125a-3p levels and activation of TP53; decreases expression of oncogenic miR-92, miR-93, and miR-106b, and increases expression of tumor suppressing miR-7-1, miR-34a, and miR-99a.	[118-125, 140-144, 152-155, 275-284, 409, 414, 415, 418, 419, 424, 504-507, 509, 510]
Chinese Qingyihuaji formula and BDL301	Inhibits NOTCH4, and JAG1, STAT3.	[126, 127]
Ascochlorin	Inhibits STAT3.	[128]
Alantolactone	Inhibits STAT3.	[129, 130]
Ethyl acetate extract from *Jiedu Xiaozheng Yin*	Suppresses polycomb complex member BMI1 and CTNNB1 signaling.	[131, 132]
Phenethyl isothiocyanate	Activates NRF2; phosphorylation of ERK and JNK; demethylates *GSTP1* promoter, inhibits HDAC activity.	[133-144, 306, 436]
Sulforaphane	Activates NRF2; phosphorylation of ERK and JNK; decreases DNMT1 and DNMT3A activities; decreases the HDAC3 and HDAC6 protein expression; increases the global histone acetylation and increases association of acetylated histone H3 on the *CDKN1A* and *BAX* gene promoters.	[133-144, 302, 303, 432-434]
Indole-3-carbinol	Inhibits NF-κB, stimulates TP53 and its targets, PUMA, APAF-1, PMAIP-1; increases ATM signaling and TP53 phosphorylation.	[148, 437]
Cucurbitacin B	Inhibits STAT3; represses DNMTs and HDACs; reactivates *CDKN1A* and *CDKN2A* expression.	[156, 333]
Eurycomanone	Inhibits NF-κB signaling through inhibition of IκBα phosphorylation.	[157, 158]
Aaptamines	Modulates AP-1, NF-κB, and TP53-dependent transcriptional activities	[159]
Codonolactone	Inhibits RUNX2.	[160]
Hirsutine	Inhibits NF-κB activation.	[161]

(Table 1) contd….

Compound Name	Epigenetic Function	References
Chebulagic acid	Inhibits NF-κB.	[162, 163]
Bergamottin	Inhibits STAT3 signaling pathway.	[164]
Ethyl acetate extract of *Annona muricata*	Activates mitochondrial-mediated signaling and suppresses nuclear translocation of NF-κB.	[165]
Isocudraxanthone K	Induces Akt, p38 MAPK, and ERK phosphorylation, as well as downregulates of HIF-1α.	[166]
Ethanolic extracts of *P. indica* root	Activates TP53.	[167]
Grifolin	Activates TP53 and upregulates of DAPK1.	[168]
Chalcones	Modulates TP53, NF-κB, STAT3, AP-1, NRF2, and CTNNB1/WNT.	[169]
Mahanine	Induces nuclear accumulation of PTEN and its interaction with TP53/TP73 proteins.	[170, 171]
Dehydroleucodine	Induces the levels of total TP73 and phosphorylated TP53, TP73, and γ-H2AX	[172]
Rocaglamide	Upregulates of the TP53.	[173, 174]
Anthocyanins/anthocyanidins	Suppresses DNMT1.	[266]
Genistein	Inhibits DNMT1, 3A, 3B, MBD2 activities, and reactivates *CDKN2A, MGMT, RARβ, BTG3, GSTP1,* and *WNT5A* genes; activates HAT; targets HDAC6; demethylates and acetylates histone H3-K9 at the PTEN and CYLD promoters and acetylates histone H3-K9 on the *TP53* and *FOXO3A* gene promoters through reduction of SIRT1 activity; upregulates let-7b, let-7e, miR-200b, miR-200c, miR-15a, miR-29a, miR-548b, miR-574-3p, miR-1256, miR-1296; downregulates miR-15b, -23b-3p, -27a, -125a, -125b, -145, -151, -155, -208b, -211, -223, -320, -376a, -411, -520g and -542-5p, -1260b.	[96, 260, 261, 285-289, 425, 427, 428, 512, 514, 516-524]
Quercetin	Reverses hypermethylation of *CDKN2A* gene; inhibits EP300/CBP activity and phosphorylation/ acetylation of histone H3; increases miR-16, miR-34a, 142-3p, miR-217 level.	[290, 291, 416, 417, 525-528]
Retinoic acid	Activates the *CDKN1A* gene transcription and inhibited AP-1 transcriptional activity; demethylates *RARβ2* and *PTEN* gene promoters; reduces the expression of DNMT1 and DNMT3B, while induces the expression of microRNAs targeting the DNMT proteins.	[83, 183, 309, 310, 329-332]
Z-Ligustilide	Demethylates *NRF2* gene promoter, and inhibits DNMT activity.	[334]
Kazinol Q	Inhibits DNMT activity.	[335]
Annurca apple extract	Increases TP53 expression; reduces promoter DNA methylation for *MLH1*, *ARF1*, and *CDKN2A* genes.	[337]
Psammaplin A, aerothionin, aeroplysinin-1, dienone, and bastadins	Inhibit HDAC and DNMT; decrease SIRT1 enzyme activity and reduce SIRT1 protein expression; increase the expression of a p53-induced damage-regulated autophagy modulator.	[339, 452]
Parthenolide	Inhibits NF-κB activation, promotes ubiquitination of MDM2 and activates TP53; decreases DNMT1 expression; downregulates HDAC1 protein.	[340-347, 446, 447, 452]
Verticillin A	Inhibits DNA methylation of *BNIP3* gene promoter; inhibits histone methyltransferases SUV39H1, SUV39H2, and G9a/GLP and decreases H3K9me3 levels in the *FAS* promoter.	[348, 461]
Folate, cobalamin, riboflavin, piridoxine or methionine)	Regulate the DNA methylation reaction by having a direct effect on the level of a methyl donor, SAM.	[349-355]
Trichostatin A	Inhibits HDACs.	[399]
Romidepsin	Inhibits class I HDACs.	[400, 401]
Diindolylmethane	Induces a proteasomal degradation of HDAC1, HDAC2, HDAC3, and HDAC8 proteins; increases the γH2AX level and phosphorylation of tripartite motif-containing-28 protein; upregulates let-7 microRNA, and downregulates EZH2 expression; upregulates of let-7b, let-7e, miR-200b, and miR-200c; upregulates miR-146.	[438, 511-513]

(Table 1) contd….

Compound Name	Epigenetic Function	References
Organosulfur compounds: diallyl disulfide, S-allylmercaptocysteine	Induce histone acetylation; increase a global acetylation of histones H3 and H4.	[441, 442]
Anacardic acid	Inhibits the EP300 and CBP-associated HAT activities.	[87, 453]
1-Alaninechlamydocin	Inhibits HDAC activity.	[454]
Selenium and selenoproteins	Decrease of HDAC activity and increase of histone acetylation and phosphorylation.	[456-458]
Sinapinic acid	Inhibits HDAC activity.	[459]
Chaetocin	Inhibits human histone-lysine N-methyltransferase SUV39H1.	[460]
Piceatannol	Induces miR-129 expression.	[500]
Polyphenon-60	Downregulates the expression of miR-21 and miR-27.	[508]
Triptolide	Upregulates miR-142-3p.	[528]
Minnelide	Upregulates miR-142-3p.	[529, 530]
Ellagitannin BJA3121	Upregulates miR-let-7e, miR-370, miR-373 and miR-526b, while downregulates let-7a, let-7c, let-7d microRNAs.	[532]
Olea europaea leaf extract	Modulates expression of miR-181b, miR-153, miR-145, miR-137, and let-7d.	[533]

presented information suggests that natural compounds act at the multiple targets, transcription factors and chromatin accessory proteins, DNA methyltransferase, histone acetylases and deacetylases, histone methylases and demethylases, as well as microRNAs involved in development of many human cancers (Table **1**).

Epigenetic drugs modulate the epigenetic regulatory mechanisms altered in tumor cells thereby enhancing abilities of epigenetic regulators to affect cell proliferation, migration and cell death, subsequently inducing cell cycle arrest, cell differentiation, or cell death via apoptosis, necrosis, autophagy or mitotic catastrophe in tumor cells, as well as tumor microenvironment, as reviewed elsewhere [550]. Thus, specific natural compounds might affect various protein targets implicated in epigenetic regulation of gene expression at the global and specific levels. However, further in-depth studies needed to define the contribution of epigenetic alterations induced by natural compounds in various human cancers. Better understanding of the epigenetic targets and pathways altered by natural compounds is required to generate novel strategies in anticancer chemotherapeutics, including their combinations with other anticancer biomolecules, such as microRNAs.

LIST OF ABBREVIATIONS

AP = Activator Protein

ARHI = Aplasia Ras Homolog Member I

ARHGDIA = Aplysia RAS-Related Epididymis Secretory Sperm Binding Protein

APAF = Apoptotic Protease Activating Factor

ATM = Ataxia Telangiectasia Mutated

ATR = ATM and Rad3 Related

CREBBP = cAMP Response Element-binding Factor (CREB)-binding Protein

C/EBPα = CCAAT/Enhancer Binding Protein alpha

CDKN1A = Cyclin-Dependent Kinase iNhibitor

CLDN2 = Claudin-2

DAPK = Death-Associated Protein Kinase

DNMT = DNA Methyltransferase

EP300 = E1A Binding Protein 300

EGFR = Epidermal Growth Factor Receptor

EZH = Enhancer of Zeste Homolog

ERK = Extracellular Signal-Regulated Kinase

FBW7 = F-Box and WD Repeat Domain Containing-7

ID4 = Inhibitor of Differentiation 4

IRF = Interferon Regulatory Factor

JNK = c-Jun N-terminal Kinases

HAT = Histone AcetylTransferase

HDAC = Histone DeACetylase

HIF = Hypoxia-inducible Factor

KLF = Krüppel-Like Factor

LSD = Lysine-Specific Demethylase

MMP2 = Matrix MetalloProteinase-2

MAPK = Mitogen-Activated Protein Kinase

MBD = Methyl-CpG-Binding Domain

MDM2 = Mouse Double Minute 2 Homolog

MITF = MIcrophthalmia-associated Transcription Factor

MAX = MYC-Associated factor X

MCM2 = Nuclear Factor-kappaB, MiniChromosome Maintenance-2

MTA1 = MTA2 Metastasis Associated 1 Family, Member 1

MTA2 = MTA2 Metastasis Associated 1 Family, Member 2

MLH1 = MutL Homolog-1

MGMT = O^6-MethylGuanine DNA MethylTransferase, NF-κB

NRF2 = Nuclear factor erythroid-2 (NF-E2)-Related Factor 2

NuRD = Nucleosome Remodeling Deacetylase complex

PCNA = Proliferating Cell Nuclear Antigen

PTEN = Phosphatase and TENsin Homolog

PMAIP = Phorbol-12-Myristate-13-Acetate-Induced Protein

PRMT = Protein aRginine MethylTransferase

PDCD4 = ProgrammeD Cell Death Protein 4

PUMA = TP53 Upregulated Modulator of Apoptosis

RECK = REversion-inducing-Cysteine-rich Protein with Kazal Motifs

RB = Retinoblastoma Protein

RAR = Retinoic Acid Receptor

RUNX = Runt-related Transcription Factor

SAM = S-adenosyl-L-methionine

STAT = Signal Transducer and Activator of Transcription

SOX17 = SRY-Related HMG-BOX Transcription Factor-17

SREBP = Sterol Regulatory Element-Binding Protein

TIMP3 = Tissue Inhibitor of matrix MetalloProteinase-3

TP53 = Tumor protein p53

UHRF = Ubiquitin-like, Containing PHD and RING Finger Domains

UTR = Untranslated Region

VIM = Vimentin

WT = Wilms' Tumor

ZEB1 = Zinc Finger E-Box Binding Homeobox 1

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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