Food and Chemical Toxicology 123 (2019) 574–594

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

An overview of epigenetic agents and natural nutrition products targeting DNA methyltransferase, histone deacetylases and microRNAs

Deyu Huang[a], LuQing Cui[a], Saeed Ahmed[a], Fatima Zainab[b], Qinghua Wu[c], Xu Wang[b,**], Zonghui Yuan[a,b,*]

[a] The Key Laboratory for the Detection of Veterinary Drug Residues, Ministry of Agriculture, PR China
[b] Laboratory of Quality & Safety Risk Assessment for Livestock and Poultry Products (Wuhan), Ministry of Agriculture, PR China
[c] College of Life Science, Institute of Biomedicine, Yangtze University, Jingzhou, 434025, China

ARTICLE INFO

Keywords:
Epigenetic therapy
DNMT
HDAC
microRNA
DNA methylation
Histone modifications

ABSTRACT

Several humans' diseases such as; cancer, heart disease, diabetes retain an etiology of epigenetic, and a new therapeutic option termed as "epigenetic therapy" can offer a potential way to treat these diseases. A numbers of epigenetic agents such as; inhibitors of DNA methyltransferase (DNMT) and histone deacetylases (HDACs) have grew an intensive investigation, and many of these agents are currently being tested in a clinical trial, while some of them have been approved for the use by the authorities. Since miRNAs can act as tumor suppressors or oncogenes, the miRNA mimics and molecules targeted at miRNAs (antimiRs) have been designed to treat some of the diseases. Much naturally occurring nutrition were discovered to alter the epigenetic states of cells. The nutrition, including polyphenol, flavonoid compounds, and cruciferous vegetables possess multiple beneficial effects, and some can simultaneously change the DNA methylation, histone modifications and expression of microRNA (miRNA). This review mainly summarizes the information of epigenetic agents of DNMTs and HDACs inhibitors, miRNA mimics and antimiRs, as well as the natural nutrition. In addition, some future perspectives related to the epigenetic therapy are also included.

1. Introduction

Currently, the field of "epigenetics" has been an exciting and rapidly growing area of research, and a consensus definition of epigenetics: "an epigenetic trait is a stably inherited phenotype resulting from changes in a chromosome without alterations in the DNA sequence" was arrived in 2008 at a Cold Spring Harbor meeting (Berger et al., 2009). In general, epigenetic modifications include DNA methylation, histone modifications, nucleosome positioning and regulation of non-coding RNAs (long intergenic noncoding RNA (lincRNA) and miRNA) (Portela and Esteller, 2010), among which DNA methylation, histone modifications and expression of lincRNA or miRNA have got much attention. It is now known that DNA methylation is mediated by DNA methyltransferase (DNMT) family of enzymes, including DNMT1, 2, 3a, 3b and 3l. But only DNMT1, 3a and 3b possess the methyltransferase activity. The DNMTs can catalyze the transfer of a methyl group from S-adenosylmethionine (SAM) to DNA, which induce hypermethylation of genes (Portela and Esteller, 2010). The balance between the acetylated/deacetylated states of histones is mediated by two different types of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). The HATs-promoted histone acetylation is related to a more relaxed euchromatin structure that is necessary for the transcriptional activation, while HDACs remove acetyl groups and suppress the gene expression (Tao et al., 2014).

Additionally, numerous human diseases such as: cancers, obesity, diabetes, aging, cardiovascular disease, neurological and neurodegenerative disorders, autoimmune disease, infectious disease, allergic disease have been linked with epigenetic aberrations (Portela and Esteller, 2010; Tollefsbol, 2012). For instance, cancer cells tend to present a profoundly distorted epigenetic alterations such as a massive global loss of DNA methylation, imbalance of histone modifications or expression of oncogenic miRNAs. Global hypomethylation can promote the chromosomal instability, gene disruption and aberrant expression of oncogenes. In some cases, the hypermethylation or mutation of tumor suppressor genes (TSGs) occurs in various cancer cells, leading to the loss or reduction in its function and finally to carcinogenesis. These genes

DOI of original article: https://doi.org/10.1016/j.fct.2018.10.059
* Corresponding author. The Key Laboratory for the Detection of Veterinary Drug Residues, Ministry of Agriculture, PR China.
** Corresponding author.
E-mail addresses: wangxu@mail.hzau.edu.cn (X. Wang), yuan5802@mail.hzau.edu.cn (Z. Yuan).

https://doi.org/10.1016/j.fct.2018.10.052
Received 12 June 2018; Received in revised form 25 September 2018; Accepted 22 October 2018
Available online 05 November 2018
0278-6915/

mainly involved in DNA repair, Ras signaling, p53 network, metastasis suppressors and cell cycle/apoptosis. Also, a prominent alteration in histone modification in cancer cells is a global loss of acetylated H4K16, the active mark H3K4me3 and the repressive mark H4K20me3, and a gain in the repressive marks H3K9me and H3K27me3, which is due to aberrant expression of HATs and HDACs (Portela and Esteller, 2010). A report also revealed that miRNAs expression is generally down-regulated in tumors compared with the normal tissues (Lu et al., 2005). However, the overexpression of many oncogenic miRNAs has been found in many types of cancer and promotes the proliferation of cancer cells (Ohtsuka et al., 2015).

2. Epigenetic therapy

The fact that many of the human diseases possess an epigenetic etiology has encouraged the development of a new therapeutic option termed as “epigenetic therapy” (Egger et al., 2004). Many agents have been discovered to alter the DNA methylation, histone modification states or miRNAs expression. Several of these agents have been examined for their anti-cancer or therapeutic effects on neurological diseases. Three main epigenetic treatments are in a reliable consideration: DNMT and HDAC inhibitors and miRNA-based therapeutics. Many naturally occurring agents are also able to change the epigenetic modifications states and these agents alone or in a combination are listed as an active drug to treat various human diseases.

2.1. DNMT inhibitors

DNMT inhibitors, mainly like 5-Azacytidine (Aza) and 5-aza-2′-deoxycytidine (or decitabine, DAC) can reverse the DNA methylation, thereby overcoming the gene silencing, particularly occurred in a pathological condition. Both compounds are nucleoside analogs, and can be converted to the activated triphosphate 5-Aza-dCTP, and subsequently incorporated, in place of cytosine, into DNA (Christman, 2002). When recognized by DNMT1, these two compounds form an irreversible covalent complex with DNMT1 and leads to DNMT1 degradation and the reduction of methylation process. The Aza and DAC have been approved by the U.S. Food and Drug Administration (FDA) in 2004 and in 2006, respectively, for the treatment of myeloid dysplastic syndrome (MDS) based on an improvement in an objective response rate in the clinic (Cheishvili et al., 2015).

The main disadvantages of Aza and DAC is that they are instable in aqueous solutions and have adverse effects including gastrointestinal (nausea, vomiting, diarrhea, constipation, and anorexia) and hematologic symptoms (neutropenia, thrombocytopenia) (Kaminskas et al., 2005). To improve the stability and increase cellular the delivery, new drugs guadecitabine (SGI-110) and 5-Azacytidine-5‘-elaidate (CP-4200) were designed. It has been shown that SGI-110, a second generation DNA hypomethylating agent, possess DNA demethylating effect on tumor suppressor genes of pre-clinical hepatocellular carcinoma models (Jueliger et al., 2016) and in primates (Taverna et al., 2012). SGI-110 is being studied in a phase II clinical trial in patients with MDS (Montalban-Bravo et al., 2016) and acute myelogenous leukemia (AML) (Kantarjian et al., 2017). CP-4200, an elaidic acid ester analog of Aza, is a nucleoside transporter-independent drug. This drug shows an admirable DNA demethylating activity in AML cells (Hummel-Eisenbeiss et al., 2013) and higher anti-tumor activity than Aza in an orthotopic ALL mouse tumor model (Brueckner et al., 2010).

Other cytidine analogs that have been shown to inhibit the DNMTs activity include 5-fluoro-2‘-deoxycytidine (FdCyd), zebularine, 2‘-deoxy-N4-[2-(4-nitrophenyl)ethoxycarbonyl]-5-azacytidine (NPEOC-DAC) and 5,6-dihydro-5-azacytidine (DHAC). FdCyd has been demonstrated to inhibit the DNMTs activity in various human cancer cell lines (Morfouace et al., 2016). Since FdCyd is rapidly metabolized in vivo by cytidine deaminase (CD), a combination of FdCyd and tetrahydrouridine (THU), a CD inhibitor has been investigated clinically in patients with advanced solid tumors (Coyne et al., 2016; Morfouace et al., 2016). Zebularine is shown to possess high oral bioavailability, low toxicity and high efficacy. It is able to form a covalent but reversible complex with DNMT1 and reverse the hypermethylation of tumor suppressor genes in cancer cells (Andrade et al., 2017). NPEOC-DAC is an analog of DAC with a modification of the N4 position of the azacitidine ring that protects the exocyclic amine of DAC. However, the compound was no more potent than DAC in vivo (Byun et al., 2008).

2.1.1. Oligonucleotides

Antisense oligodeoxynucleotides as an anticancer therapy has a promising prospect. MG98, a 20-nucleic acid oligonucleotide, was designed to inhibit DNMT1 gene expression. MG98 can re-activate the expression of silenced tumor suppressor genes and inhibit the proliferation of growing cancer cells. It also induced dose-dependent reduction in tumor size in human colon and murine lung tumor xenograft models (Amato et al., 2012; Reu et al., 2005). MicroRNA-29b was found to directly interact with 3‘-untranslated regions of genes *DNMT3a* and *DNMT3b*. Furthermore, it could decrease the known trans-activator stimulatory protein 1 (Sp1) of *DNMT1* gene to down-regulate the expression of DNMT1. The repression of DNMTs in turn led to decrease in a global DNA methylation and re-activation of tumor suppressors $p15^{INK4b}$ and estrogen receptor 1 (ESR1) in AML cells (Garzon et al., 2009). Some other agents that possess the inhibitory activity on DNMTs was shown in Table 1. The chemical structures of these DNMT inhibitors were present in Fig. 1.

2.2. HDAC inhibitors

Four classes (class I, II, III and IV) of HDACs have been identified in according to functional criteria and their homology with their yeast analogs. They can be further divided into Zn^{2+}-dependent (class I, II and IV) and NAD-dependent classes (class III). Class I consists of HDAC1, 2, 3 and 8. HDAC4, 5, 7 and 9 are members of class IIa. Class IIb contains members of HDAC6 and 10. HDAC11 belongs to Class IV with some features of classes I and II. Class III members are well known as sirtuins due to their homologs to yeast SIR2 protein (Haberland et al., 2009) (see Table 2).

Increasing number of evidences has suggested that histone hypoacetylation is an important part of etiology for various clinical diseases such as cancer, heart failure and central nervous disease (Qiu et al., 2017). HDAC inhibitor (HDACi) can inhibit the activities of HDACs and restore the level of histone acetylation, thus may have the potential to treat a lot of clinical disorders (Qiu et al., 2017). Most of the current knowledge about HDACi comes from cancer biology researches. The anti-cancer activity of HDACi is generally derived from their ability to induce the apoptosis, cell cycle arrest, differentiation, senescence and to inhibit angiogenesis in different types of cancers (Zhang et al., 2017a).

According to their structural differences, HDACi can be primarily divided into four classes: hydroxamic acids (e.g. trichostatin A, vorinostat), cyclic peptides (e.g. romidepsin), benzamides (e.g. entinostat) and short chain fatty acids (e.g. valproic acid). Two successful HDACi, vorinostat and romidepsin have been approved by the U.S. FDA for the treatment of cutaneous T-cell lymphoma and peripheral T-cell lymphoma, respectively (Anonymous, 2009; Mann et al., 2007). Panobinostat is considered a first-in-line HDACi and have been approved by the U.S. FDA and European Medicines Agency (EMA) for use in combination with bortezomib and dexamethasone in patients with multiple myeloma (Laubach et al., 2015). Many other HDACi are shown to have anti-proliferative and pro-apoptotic effects in cancer cells, which make them being candidates of anti-cancer drugs. Some of them are also currently in phases of clinical trials (Table 3). The chemical structures of these HDAC inhibitors are present in Fig. 2.

Table 1
Classification of DNMTs inhibitors according to their chemical structures.

Classification	Compounds	DNMTs	Actions	Clinical Status	Reference
Nucleoside analogs	5-Azacytidine (Aza)	DNMT1, 3a and 3b	Forms a irreversible covalent complex with DNMT1 and triggers proteasome-mediated DNMT degradation. Prevents DNA synthesis at higher concentrations.	Aza was approved by the FDA in 2004 for MDS treatment.	Kaminskas et al. (2005)
	5-aza-2'-deoxycytidine (DAC)	DNMT1, 3a and 3b	Functions in a similar manner to Aza with a difference that it can only be incorporated into DNA.	DAC was also approved in 2006 for MDS treatment.	Ball et al. (2017)
	2'-deoxy-N4-[2-(4-nitrophenyl) ethoxycarbonyl]-5-azacytidine (NPEOC-DAC)	DNMT1, 3a and 3b	A NPEOC group is added to the N4 position of the azacytosine ring, which protects the azacitidine ring and can be cleaved by carboxylesterase to release DAC.	Pre-clinical studies	Byun et al. (2008)
	Guadecitabine (SGI-110)	DNMT1, 3a and 3b	SGI-110 includes a deoxyguanosine and is largely resistant to cytidine deaminase. It has a longer half-life than its active metabolite DAC.	Phase I study for MDS. Phase II study for AML. Pre-clinical study for hepatocellular carcinoma.	(Kantarjian et al., 2017; Montalban-Bravo et al., 2017)
	CP-4200	DNMT1, 3a and 3b	CP-4200 is an elaidic acid ester derivative of Aza. Its uptake is less dependent on conventional nucleoside transporters.	Pre-clinical study for AML.	Hummel-Eisenbeiss et al. (2013)
	5-Fluoro-2'-deoxycytidine (FdCyd)	DNMT1, 3a and 3b	FdCyd is a fluoropyrimidine nucleoside analog. FdCyd inhibits DNMTs activity in a way similar to AZA and DAC.	Phase I study of combination of FdCyd and THU for advanced solid tumors and brain tumors.	Morfouace et al. (2016)
	Zebularine	DNMT1, 3a and 3b	Forms a covalent, but reversible complexe between DNMT protein and zebularine-incorporated DNA.	Pre-clinical studies.	(Aranda et al., 2017; Nakamura et al., 2017; Takemura et al., 2018)
	5,6-dihydro-5-azacytidine (DHAC)	DNMT1, 3a and 3b	Restores the estrogen sensitivity in androgen-refractory tumor cells.	Pre-clinical studies.	Izbicka et al. (1999)
Oligonucleotides	MG98	DNMT1	MG98 binds with DNMT1 mRNA and interferes with its further processing and production of DNMT1.	Phase I study for high-risk myelodysplasia and AML. Phase I study for advanced solid tumors. Phase II study for metastatic renal carcinoma.	(Klisovic et al., 2008; Plummer et al., 2009; Winquist et al., 2006)
	miR29b	DNMT1, DNMT3a and 3b	MiR29b reduces the mRNA level of DNMT1, 3a and 3b. miR-29b also induces apoptosis in AML cells.	Pre-clinical studies.	(Liang et al., 2018; Starlard-Davenport et al., 2013; Yang et al., 2018)
Other small molecules	RG108	DNMT1 and DNMT3b	RG108 decreases DNMT activity, DNMT1 expression and global DNA methylation in human prostate cancer cells. Inhibits DNMT3b expression in human endometrial cancer Ishikawa cells and inhibits the promoter methylation of tumor suppressors.	Pre-clinical studies.	(Graca et al., 2014a; Yang et al., 2017a)
	SGI-1027	DNMT1, DNMT3a	SGI-1027 is a quinolone-based compound, and can inhibit the DNMT1 and 3a activity and result in decreased methylation at TSG CpG islands and corresponding gene up-regulation.	Pre-clinical studies.	Datta et al. (2009)
	Nanaomycin A	DNMT3b	Nanaomycin A selectively inhibits DNMT3b and reactivates the expression of RASSF1A in human cancer cells.	Pre-clinical studies.	(Caulfield and Medina-Franco, 2011; Nakamae et al., 2018)
	Procainamide	DNMT1	Procainamide is an antiarrhythmic drug that is shown to inhibit the expression of DNMT1 in rats and in cells.	Pre-clinical studies.	Shih et al. (2016)
	Procaine	DNMT1, DNMT3a	Reduces DNMT1 activity, and results in CpG island demethylation of the gene aquaporin-5 in human salivary gland ductal cells. Represses the activity of DNMT1 and DNMT3a, reduces the DNA methylation in the promoter regions of CDKN2A and RAR genes.	Pre-clinical studies.	(Li et al., 2018c; Wu et al., 2018)
	Hydralazine	DNMT1, 3a and 3b	Decreases the mRNA levels of DNMT1, 3a and 3b. Decreases the promoter methylation levels of TSGs in prostate cancer cells.	Pre-clinical studies.	(Graca et al., 2014b; Singh et al., 2013)
	Mythramycin A	DNMT1	Reduces the CpG island methylation of TSGs, and results in DNMT1 protein depletion and decreases metastasis ability of lung cancer cells.	Pre-clinical studies.	Lin et al. (2007)
	Olsalazine	DNMT1, 3a and 3b	Inhibits the DNMTs activity, and mimics the action of 5-aza-2'-deoxycytidine.	Pre-clinical studies.	Mendez-Lucio et al. (2014)
	Mahanine	DNMT1, DNMT3b	Induces DNMT1 and 3b degradation but not DNMT3a via Akt inactivation. Restores the RASSF1A expression of by inducing the demethylation of its promoter in prostate cancer cells.	Pre-clinical studies.	Agarwal et al. (2013)
	NSC 14778	DNMT1 and DNMT3b	Selectively inhibits both DNMT1 and DNMT3b activity in biochemical assays.	Pre-clinical studies.	Aldawsari et al. (2016)
	NSC 622444, 408488, 137546, 56071, 319745, 106084	DNMT1	This six compounds selectively inhibit DNMT1 activity in biochemical assays.	Pre-clinical studies.	Hassanzadeh et al. (2017)

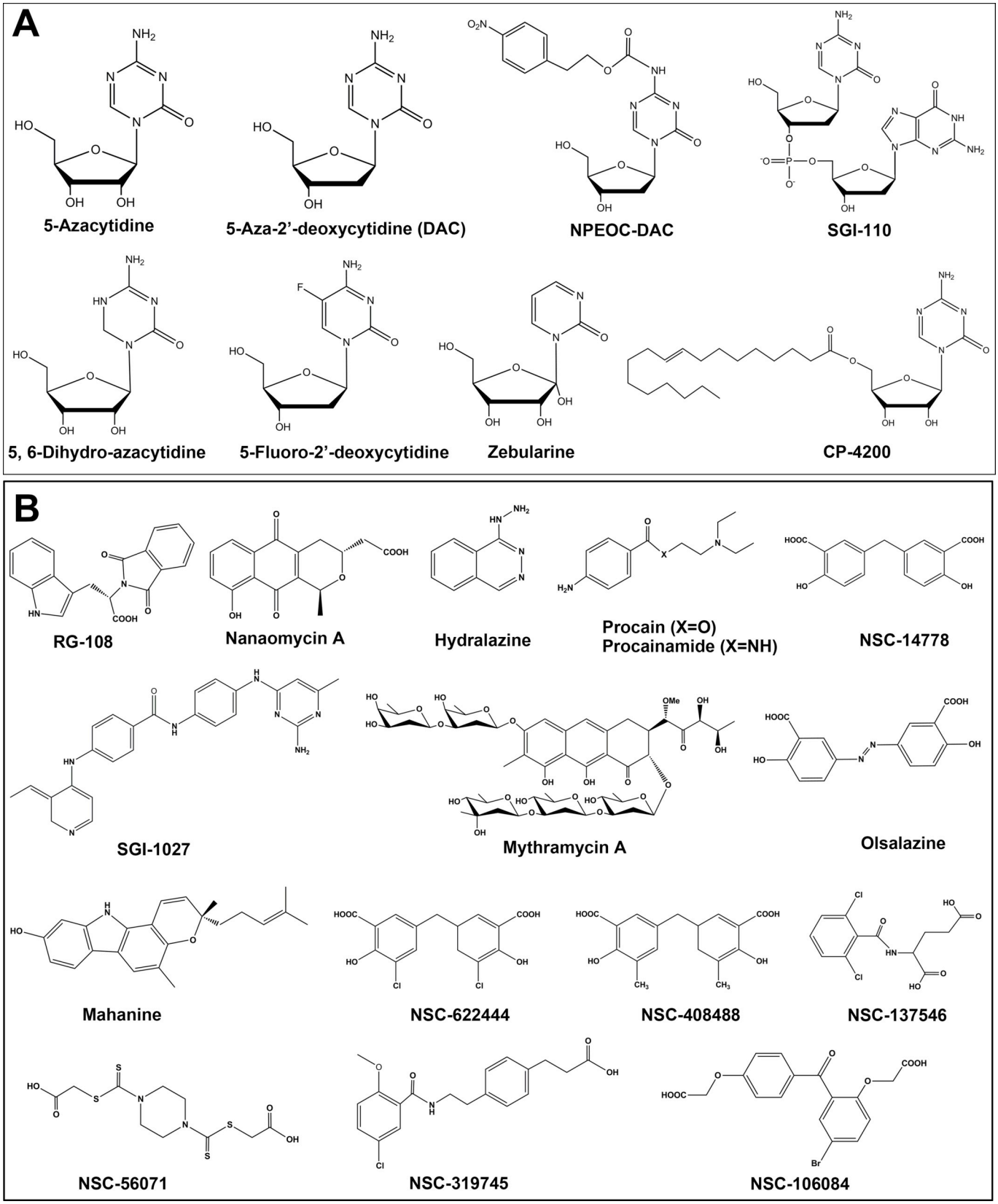

Fig. 1. The chemical structures of DNMT inhibitors. (A) Nucleoside analogs that can be incorporated into DNA to inhibit DNMTs activity. (B) Non-nucleoside DNMTs inhibitors (Foulks et al., 2012).

Table 2
Classification of HDACs.

Zn^{2+}-dependent			NAD-dependent
class I HDAC1, 2, 3, 8	class II IIa: HDAC4, 5, 7 and 9 IIb: HDAC6 and 10	class III HDAC11	class IV sirtuins 1-7

2.3. MicroRNA modulators

miRNA is a type of small non-coding RNA molecule (20–25 nucleotides) with a function in RNA silencing and post-transcriptional regulation of gene expression. The studies of last decades have greatly contributed to our understanding of the normal functioning of miRNA in eukaryotic cells, as well as the biological roles of miRNAs in many human diseases, such as various cancers, heart, kidney and nervous system diseases and obesity. Since the miRNAs are frequently over-expressed or down-regulated in various cancers, the therapeutics targeting the miRNAs by inhibiting the oncomiRs or increasing the tumor suppressive miRNAs hold some promises in treating cancers. Some miRNA-based therapeutics are being tested in clinical trials. However, some aspects like possible side off-target effects, dosage issues and effective in vivo delivery tool need to be considered when applying such approach.

2.3.1. MiRNA mimics

MiRNA mimics are synthetically derived double-stranded RNAs that mimic endogenous mature miRNAs. Given that a numbers of miRNAs such as miR-1, let-7 family, miR-15/16 cluster, miR-29b, miR-30b, miR-33a, miR-34a, miR-143 and miR-145, miR-200 family, miR-302, miR-506, miR-520 and miR-596 have revealed a tumor suppressive function, the therapeutics based on miRNA replacement targeting these tumor suppressive miRNAs hold some promises in cancer treatment. Some

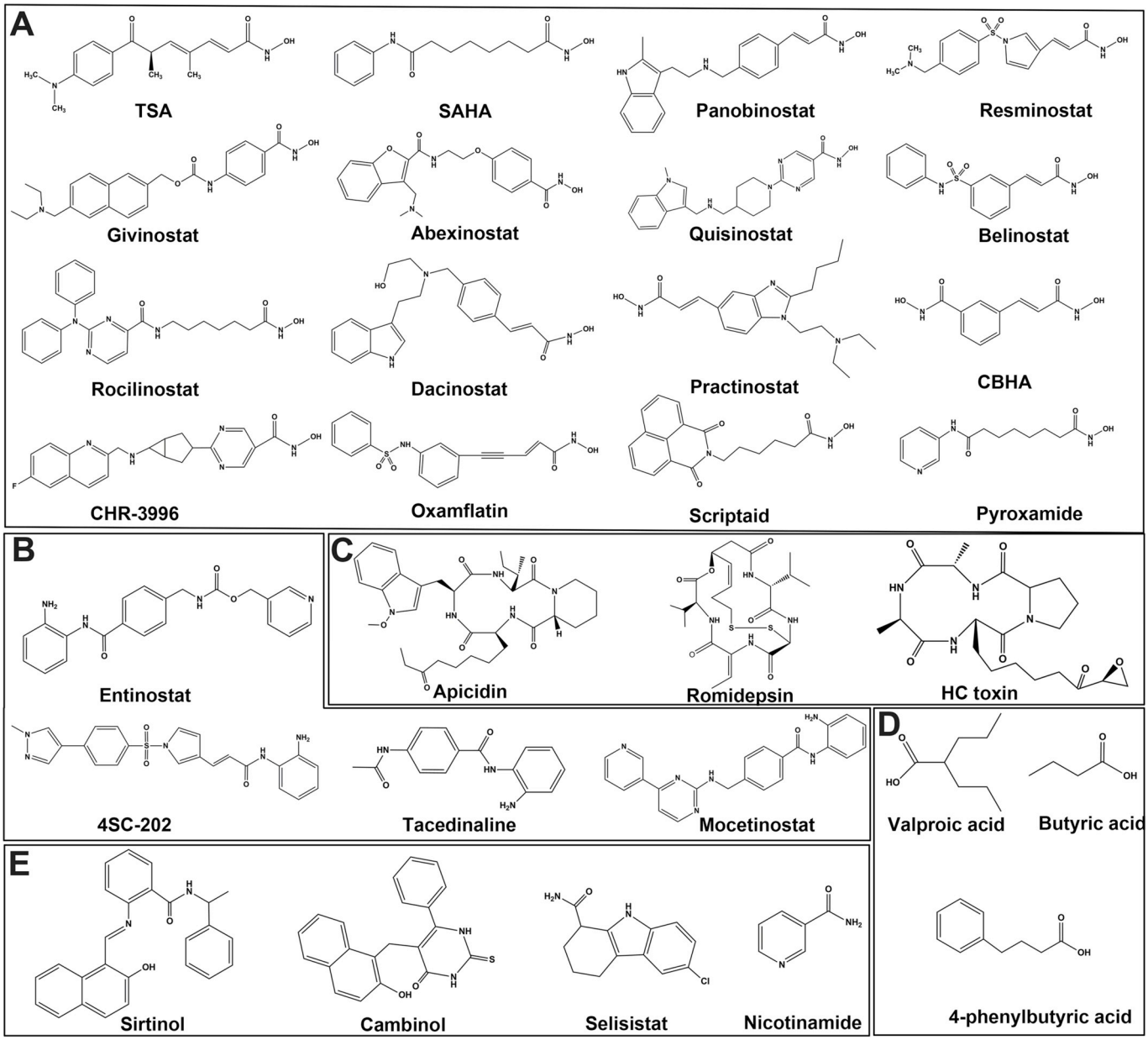

Fig. 2. The chemical structures of HDAC inhibitors. (A) Hydroxamic acid HDAC inhibitor. (B) Benzamides derivatives as HDAC inhibitors. (C) Cyclic peptide HDAC inhibitors. (D) Short-chain fatty acids as HDAC inhibitors. (E) Sirtuins inhibitors.

Table 3
Classification of HDACs inhibitors according to their chemical structures.

Classification	Compounds	HDAC	Actions	Clinical Status	Reference
Hydroxamic acids	Trichostatin A (TSA)	Pan	Reaches the active site of HDAC, chelates Zn^{2+} and inhibits HDAC activity. Induces autophagy, cell cycle arrest, ER stress, PI3K/Akt/mTOR inhibition and apoptosis. Regulates innate immunity and tumor antigen recognition-associated genes.	Pre-clinical	Chen et al. (2017a)
	Suberanilohydroxamic acid or Vorinostat (SAHA)	Pan	Works in a way similar to TSA. Causes accumulation of acetylated histones. Induces cell cycle arrest and apoptosis in breast cancer cells and other types of cancer cell.	Approved for cutaneous T-cell lymphoma (CTCL). Phase I/II trials of SAHA in combination with many other drugs for treatment of a variety of solid tumors like diffuse large or relapsed or refractory B-cell lymphomas, breast cancers, non-small cell lung cancer, mantle cell lymphoma and relapsed or refractory indolent non-Hodgkin's lymphoma.	(Hanke et al., 2016; Spurgeon et al., 2014; Xu et al., 2018)
	Belinostat (PXD101)	Pan (class I, II and IV)	Belinostat includes a hydroxamate region that chelate the Zn^{2+} and inhibit HDAC activity.	Approved for peripheral T-cell lymphoma (PTCL). Phase I/II trials of belinostat with other drugs for small cell lung cancer, soft tissue sarcomas, acute myeloid leukemia and thymic epithelial tumors.	(Balasubramaniam et al., 2018; Campbell and Thomas, 2017; Kirschbaum et al., 2014; Vitfell-Rasmussen et al., 2015)
	Panobinostat (LBH589)	Pan	Inhibits PI3K/AKT and NF-κB pro-survival pathways and activate ERK intrinsic apoptotic pathway. Decreases phospho-EGFR, phospho-ERK and phospho-AKT level and increases p21 and p53 expression. Induce apoptosis and cell cycle arrest in various cancer cells.	Panobinostat is approved in combination with the anti-cancer drug bortezomib and the corticoid dexamethasone for multiple myeloma.	(Greve et al., 2015; Sivaraj et al., 2017)
	Givinostat (ITF2357)	Pan	Inhibits class I and II HDACs, and reduces pro-inflammatory cytokines TNF, IL-1α, IL-1β and IL-6. Anti-angiogenic, anti-neoplastic activity against both systemic juvenile idiopathic arthritis and myeloproliferative neoplasms.	Phase II clinical trials for relapsed leukemia and multiple myeloma.	(Galli et al., 2010; Regna et al., 2014; Savino et al., 2017)
	Resminostat (4SC-201)	Pan (class I, II and III)	Inhibits Akt signaling pathway, decreases subsequent phosphorylation of 4E-BP1 and p70S6k. Induces apoptosis by increasing Bim and Bax, decreasing Bcl-xL, and activation of caspases 3, 8, and 9.	Phase I/II clinical trials with sorafenib for hepatocellular carcinoma. Phase I/II clinical trial for K-ras mutated advanced colorectal carcinoma. Phase II clinical trial for relapsed or refractory Hodgkin's lymphoma.	(Bitzer et al., 2016; Walewski et al., 2011)
	Abexinostat (PCI-24781)	Pan	Induces apoptosis of cancer cells. Inhibits RAD51 and repair of double-strand DNA breaks in gastric cancer cells and pediatric glioblastoma cells. Inhibits ErbB2 to reduce cell growth of biliary tract cancer cells.	Phase II clinical trial for B-cell lymphoma. Phase II clinical trial for relapsed or refractory follicular lymphoma and mantle cell lymphoma.	(Deutsch et al., 2017; He et al., 2014; Vey et al., 2017)
	Quisinostat (JNJ-26481585)	Pan (class I and II)	Induces caspase activation, up-regulation of p21, Bax/Bak activation and mitochondria-dependent apoptosis in myeloma cells. Increases histone H3 acetylation, tumor growth inhibition in colon carcinoma and leukemia cells.	Phase I clinical trial for relapsed multiple myeloma, non-small cell lung cancer, ovarian cancer Phase II clinical trial for recurrent platinum resistant high grade serous epithelial ovarian cancer (peritoneal or fallopian tube carcinoma). Phase II clinical trial for Seezary syndrome.	(Child et al., 2016; Fedyanin et al., 2016; Moreau et al., 2016)
	Rocilinostat (ACY 1215)	HDAC6	Binds to HDAC6, thereby disrupting the Hsp90 protein chaperone system through hyperacetylation of Hsp90. Induces acetylation of α-tubulin at lower dose and triggers acetylation of lysine on histone H3 and H4 at higher doses.	Phase II clinical trials for relapsed or refractory multiple myeloma in combination with pomalidomide, unresectable or metastatic breast cancer. Phase I/II clinical trials for relapsed or refractory lymphoid malignancies.	(Onishi et al., 2017; Raje et al., 2012)
	Pracinostat (SB939)	class I, II, IV	Inhibits HDAC activity, resulting in acetylated histones accumulation, chromatin remodeling, TSGs transcription, and apoptosis of tumor cells.	Phase II trial of pracinostat plus azacitidine in elderly patients with AML and patients with previously untreated myelodysplastic syndrome. Phase II trial for prostate cancer.	(Eigl et al., 2015; Takahashi et al., 2017)
	CHR-3996	class I (HDAC 1, 2, and 3)	Up-regulates HSP70 and down-regulates anti-apoptotic Bcl-2. Up-regulates BIRC3, an inhibitors of NF kappa B. Activates p53 and caspase to induces apoptosis.	Phase I trial of CHR-3996 plus tosedostat for relapsed, refractory multiple myeloma. Phase I trial for advanced/metastatic solid tumors.	(Banerji et al., 2012; Popat et al., 2016)

(*continued on next page*)

Table 3 (*continued*)

Classification	Compounds	HDAC	Actions	Clinical Status	Reference
	Dacinostat (LAQ824)	Pan	Increases p21 expression to inhibit cell growth of non-small cell lung carcinoma and colon cancer cells. Activates mitochondria-dependent apoptosis in cancer cells. Induces histone H3 and H4 acetylation, and HSP90 acetylation and degradation of its cargo oncoproteins.	Phase I trial for advanced solid tumors and hematologic malignancies.	(de Bono et al., 2008; Rowinsky et al., 2005; Wang et al., 2006; Zhu et al., 2015)
	Pyroxamide (NSC696085)	HDAC1	Induces cell cycle arrest and apoptosis, and increases acetylation levels in histones H2A, H2B, H3 and H4 in murine erythroleukemia cells (MEL). Increases histone acetylation and expression of p21 $^{WAF1/CIP1}$, leading to tumor growth inhibition in mice prostate tumors.	Pre-clinical.	Butler et al. (2001)
	M-carboxycinnamic acid *bis*-Hydroxamide (CBHA)	HDAC1 and HDAC3	Causes accumulation of acetylated histone H3 and H4 in MEL cell and neuroblastoma cells. Activates BH3-only protein Bmf transcription to mediate disruption of $\Delta\psi$m, DNA fragmentation and apoptosis in cancer cells.	Pre-clinical.	(Song et al., 2014; Takai et al., 2015)
	Oxamflatin	Pan	Inhibits DNA synthesis and cell proliferation, down-regulates c-Myc, CDK4 and E2F1 expression and phosphorylation of retinoblastoma (Rb) protein, and up-regulates p21 and E-cadherin expression in cancer cells.	Pre-clinical.	(Faghihloo et al., 2016; Wang et al., 2016b)
	Scriptaid	pan	Activates JNK pathway, increases p21 and p27 to induce apoptosis, increases γ-H2AX-associated DNA damage and Ras activity, and decreases telomerase activity in glioblastoma cells and myeloma. Increases α-estrogen receptor mRNA levels in breast cancer cells.	Pre-clinical.	(Keen et al., 2003; Yao et al., 2018)
Cyclic peptides	Romidepsin (FK228)	Class I (HDAC1 and 2)	Induces up-regulation of p21 and down-regulation of cyclin D1, inhibition of CDK, dephosphorylation of Rb and growth arrest in HeLa cells. Induces HDAC inhibition, H3 and H4 acetylation and mitochondria-dependent apoptosis in various cancer cells.	Approved for cutaneous T-cell lymphoma.	(Duvic et al., 2018; Furumai et al., 2002)
	Apicidin	Class I (HDAC3, 4, 6)	Decreases HIF-1a and HDAC4 expression, blocks cell migration and invasion, activates mitochondria-dependent apoptosis. Induces autophagy by inactivation of ERK and AKT/mTOR and activation of JNK pathway.	Pre-clinical.	(Ahn et al., 2012, 2015; Zhang et al., 2017b)
	Helminthosporium carbonum toxin (HC-toxin)	HDAC1	Increases estrogen receptor level to induce apoptosis in human breast cancer cells. Decreases transcription of cell cycle regulators of Rb tumor suppressor network.	Pre-clinical.	(Deubzer et al., 2008; Joung et al., 2004)
Benzamides	Entinostat (MS-275)	HDAC1 and HDAC3	Induces expression of miR-125a, miR-125b, and miR-205, thereby down-regulation of erbB2/erbB3 and apoptosis in breast cancer cells. Increases p21$^{WAF1/CIP1}$, decreases Foxp3 expression through STAT3 acetylation in multiple human tumor cells.	Phase II trial for Hodgkin's lymphoma. Phase II trial in combination with 5-Aza for advanced breast cancer and metastatic colorectal cancer, and for advanced non-small-cell lung cancer (in combination with erlotinib).	(Azad et al., 2017; Connolly et al., 2017; Johnson et al., 2016; Younes et al., 2011a)
	Tacedinaline (CI-994)	Class I (HDAC 1, 2, 3)	Inhibits cell growth, induce cell cycle arrest at G0/G1 phase, and apoptosis in mutiple cancer cells.	Phase I trial in combination with gemcitabine or carboplatin or paclitaxel for advanced solid tumors. Phase II trial in combination with gemcitabine for advanced pancreatic cancer	(Gediya et al., 2008; Pauer et al., 2004)
	4SC-202	Class I (HDAC 1, 2, 3)	Induces cell cycle arrest, AKT inhibition and mitochondria-dependent apoptosis. Induces hyper-acetylation of histone H3. Interferes with normal development of mitotic spindle. Activates ASK1-dependent apoptosis.	Pre-clinical.	(Fu et al., 2016; Huang et al., 2016)
	Mocetinostat (MGCD0103)	HDAC1, 2, 3 and 11	Activates miR-31, induces hyperacetylation of histones, decreases E2F6, induces cell cycle arrest and apoptosis in various human cancer cell lines. Activates PI3K/AKT/mTOR pathway which results in autophagy in chronic lymphocytic leukemia cells.	Phase II trials for Hodgkin's lymphoma and refractory follicular lymphoma. Phase II trials in combination with 5-Aza for myelodysplastic syndrome. Phase II trials for relapsed or refractory lymphoma. Phase I/II trials in combination with gemcitabine for advanced pancreatic cancer and other advanced solid tumors. Phase I/II trials in combination with durvalumab for advanced solid tumors and non-small cell lung cancer.	(Chan et al., 2018; Luger et al., 2013; Younes et al., 2011b)

(*continued on next page*)

Table 3 (*continued*)

Classification	Compounds	HDAC	Actions	Clinical Status	Reference
Short chain fatty acids	Valproic acid	Class I and IIa	Increases p21 level and induces cell-cycle arrest and apoptosis. Causes histones H3 and H4 hyperacetylation, inhibits HDAC activity, induces HSP90 dysfunction.	Approved for epilepsy, bipolar disorders and migraine.	(Li et al., 2015c; Mawatari et al., 2015)
	Butyric acid	Class I, II (HDAC1, 2, 3, 8)	Inhibits HDAC activity, causes an increase of histone H3 lysine 9 and 18 and histone H4 lysine 16 acetylation.	Phase II clinical trials	de Conti et al. (2013)
	4-Phenylbutyric acid	Class I, II	Increases histone acetylation levels by inhibiting HDAC activity. Inhibits proliferation of tumor cells.	Phase I study in combination with Aza for patients with refractory solid tumors.	(Lin et al., 2009; Shi et al., 2018)
Sirtuins inhibitors	Nicotinamide	All class III	Nicotinamide binds in a conserved pocket in the SIRT structures to inhibit the SIRT enzymatic activity.	Phase III clinical trial for laryngeal cancer. Phase II study for skin cancer.	(Chen et al., 2016a; Janssens et al., 2012; Panuganti et al., 2008)
	Sirtinol	SIRT 1 and 2	Inhibits phosphorylation of Raf-1, MEK, ERK, JNK and p38 MAPK. Blocks activation of Ras. Inhibits the Sirt1 to enhance the p53 acetylation to enhance cell death.	Preclinical.	(Ota et al., 2006; Zhou et al., 2014b)
	Cambinol	SIRT 1 and 2	Induces hyperacetylation of BCL6 and p53, leading to apoptosis in Burkitt lymphoma cells.	Preclinical.	Mahajan et al. (2014)
	Selisistat (EX-527)	SIRT 1	Enhances p53 acetylation by inhibiting SIRT1 activity.	Phase II clinical trials for Huntington. Disease, glaucoma.	(Ceballos et al., 2018; Reilmann et al., 2014)
Others	AR-42	Pan	Induces histone hyperacetylation and $p21^{WAF/CIP1}$ overexpression. Decreases phospho-Akt, Bcl-xL and activates caspases pathway, induces growth inhibition, cell cycle arrest, apoptosis and autophagy in cancer cells.	Phase I study in patients with multiple myeloma and T- and B-cell lymphomas, solid tumors including nervous system tumors.	Chen et al. (2017b)

Note: Δψm: mitochondrial membrane potential; Pan indicates not specific to certain class of HDAC.

mimics of tumor suppressive miRNAs have been tested in preclinical studies, and even entered the phase I clinical trial. For example, MRX34 is a liposome-encapsulated miR-34a mimic, and is currently being tested in a phase I clinical trial for advanced solid tumors and haematological malignancies (Beg et al., 2017; Kelnar et al., 2016). In multiple orthotopic murine models of liver and lung cancer, MRX34 treatment results in a significantly increased miR-34a level in tumors, decreases the expression of multiple target genes, and inhibits the tumor growth with a dose-dependent manner (Daige et al., 2016; Trang et al., 2011). Some other miRNA mimic-based therapeutics are shown in Table 4.

2.3.2. AntimiRs

AntimiRs are a class of chemically synthetic single stranded oligonucleotides and designed to bind directly to the targeted miRNA by complementary mechanism which blocks the function of the corresponding miRNA. AntimiRs with a 2'-O-methoxyethyl modification are called antagomiR (Rupaimoole and Slack, 2017). Many miRNAs such as miR-10b, miR-17, miR-21, miR-23b, miR-27a, miR-100, miR-125b, miR-155, miR-210, miR-212, miR-17/92 cluster, miR-221 and miR-222 have been demonstrated to possess oncogenic functions (Gambari et al., 2016; Rupaimoole and Slack, 2017). The anti-cancer strategy based on the suppression of these oncogenic miRNAs has been demonstrated to be feasible in animal models of various cancers, ischemic stroke, asthma, diabetes, viral infection, allergic inflammation, cardiovascular disease and hypertrophic scarring (Guo et al., 2017; Lee et al., 2017; Ma et al., 2010; Yang et al., 2017b). So far, several antagomir-based therapeutics, including miravirsen, RG-101, RG-125 and MRG-106 have entered clinical trials for treating chronic hepatitis C infection, type 2 diabetes and cutaneous T cell lymphoma and mycosis fungoides (Table 4).

2.3.3. MiRNA sponge

The inhibition of miRNA can also be attained through miRNA sponges. miRNA sponge was firstly termed as a competitive miRNA inhibitors that are regulatory RNAs containing multiple, tandem binding sites to a miRNA of interest (Bak and Mikkelsen, 2014). Such miRNA sponge can bind to miRNAs and competitively sequester them, thereby up-regulates miRNA target gene expression. This sponge mainly includes lncRNAs, circular RNAs (circRNAs) and pseudogene transcripts, and can be used as a tool for identifying miRNA targets and studying the function by investigating the loss-of function phenotypes (Thomson and Dinger, 2016). For example, the lncRNAs, H19, HULC, CCAT1, NEAT1, UCA1, MIR31HG, PCGEM1, linc00305 expressed respectively in gastric cancer, liver cancer, colon cancer, glioma cells, urothelial carcinoma and lung cancer, pancreatic cancer, prostate cancer and human umbilical vein endothelial cells has been reported to act as a sponge of miR-141, miR-372, let-7, miR-449b-5p, miR-16 and miR-193a-3p, miR-193b, miR-770 and miR-136 to promote the cancer progression or inhibit apoptosis (Deng et al., 2015; Li et al., 2015b, 2016; Liang et al., 2015; Liu et al., 2016c; Wang et al., 2010; Yang et al., 2016). The miRNA sponge effects by circRNAs have been a hotspot research recently. The circRNAs mostly originate from a non-canonical form of alternative head-to-tail splicing. They are much more stable and less susceptible to exonuclease digestion than linear transcripts, which make them ideal candidates as a miRNA sponge (Kulcheski et al., 2016). So far, at least four circRNAs have been shown to possess miRNA sponge effect. They include: circRNA CDR1-as/ciRS-7 acts as sponge of miR-7 in central nervous system (Kumar et al., 2017a). Sry-derived circRNA is a sponge of miR-138 in testis (Hansen et al., 2013). CircRNA ITCH acts as sponges of miR-7, miR-17 and miR-214 in oesophageal squamous cell carcinoma (Li et al., 2015a). CircRNA 001569 is a sponge of miR-145 in the colorectal cancer (Xie et al., 2016).

2.3.4. MiRNA masking

miRNA masking is another approach to inhibit the miRNA function, which is through using a modified single-stranded oligoribonucleotide.

Table 4
Typical examples of miRNA therapeutics in clinical trials.

Name	miRNA target	Clinical status	References
Miravirsen	AntimiR-122	Phase II clinical trial hepatitis C virus infection	van der Ree et al. (2016)
RG-101	AntimiR-122	Phase II clinical trial for chronic hepatitis C	van der Ree et al. (2017)
RG-125	AntimiR-103/107	Phase I clinical trial for type 2 diabetes	Wagner et al. (2015)
MRG-106	AntimiR-155	Phase I clinical trial for cutaneous T cell lymphoma and mycosis fungoides	Querfeld et al. (2017)
MRG-201	miR-29 mimic	Phase II clinical trial for subjects with a predisposition for keloid formation. Phase I clinical trial for scleroderma	Gallant-Behm et al. (2017)
MesomiR-1	miR-16 mimic	Phase I clinical trial for malignant pleural mesothelioma and advanced non-small cell lung cancer	van Zandwijk et al. (2015)
MRX34	miR-34 mimic	Phase I clinical trial for multiple solid cancers	Beg et al. (2017)

A miRNA masking does not directly interact with its target miRNA, but binds to the miRNA binding site of a target mRNA by fully complementary mechanism. In this way, the miRNA masking covers up the access of its target miRNA to the binding site of mRNA (Wang, 2011). Such miRNA masking has been demonstrated to be useful in vitro and can exert an inhibitory effect against miRNA (Murakami and Miyagishi, 2014; Obad et al., 2011).

2.3.5. Chemical modifications and delivery systems of miRNA-based therapeutics

One of the major challenges for miRNA-based therapeutics is the degradation of oligonucleotides by nucleases. To improve the stability and increase the efficacy of miRNA-based therapeutics, two different strategies have been developed. One strategy is to introduce the chemical modifications into targeted oligonucleotides, such as 2‘-deoxy, 2‘-O-methyl, cholesterol-conjugated, locked nucleic acid (LNA), peptide nucleic acids (PNA), 2‘-flouro, 2‘-O-methoxyethyl and phosphorothioate backbone modification (Hodjat et al., 2017). Another strategy is to develop delivery vehicles to increase the efficacy of in vivo delivery. Such delivery vehicles, including liposomes, polymeric micelles and vesicles, nanoparticles and dendrimers are under development (Rupaimoole and Slack, 2017). Viral vectors are now getting much attention due to its high efficiency and low pathogenicity, and the most representative among the viral vectors is adeno-associated virus (AAVs). The AAV vectors containing the sequence of a mature miRNA can persistently and highly expressed in target cells (Hodjat et al., 2017). Exosomes are another promising candidate for exogenous oligonucleotides delivery to target cells. Exosomes are small membrane bound vesicles that are secreted into the extracellular environment by various types of cell, and established intercellular communication by transporting proteins, lipids, and RNAs to recipient cells. The exogenous RNAs like therapeutic small interfering RNAs and miRNAs can be introduced into exosomes, and subsequently delivered to the target cells to cause selective gene silencing (Wahlgren et al., 2016).

3. Naturally bioactive compounds

3.1. Folic acid and vitamin B12

Folic acid (vitamin B_9) and vitamin B_{12}, two water-soluble vitamins, are required for synthesis of methionine and SAM. SAM is a universal methyl donor required for the maintenance of methylation patterns in DNA. Deficiencies in folic acid and vitamin B_{12} will inhibit the synthesis of SAM, accordingly reduce the DNA methylation. This will result in single- and double-stranded DNA breaks and micronucleus formation, intrauterine growth retardation, impaired fatty acid oxidation in liver and heart (Fenech, 2012) and interfere with fetal programming and brain development with epigenetic mechanisms (McGee et al., 2018). A clinical investigation also showed a significant correlation between serum folic acid and vitamin B_{12} levels with DNA methylation of tumor suppressor and repair genes *p16*, *MLH1*, and *MGMT* in elderly Chileans (Sanchez et al., 2017).

3.2. Polyphenol compounds

Dietary polyphenols have been shown to have an impacts on intracellular signaling networks, cell proliferation and apoptosis, and modulate carcinogenesis in certain populations (Omidian et al., 2017). These compounds have the potential to reverse adverse epigenetic states of DNA methylation, affect the histone modifications and change the miRNAs expression. They can re-activate the expression of TSGs and repress oncogenes expression through epigenetic mechanisms (Zhu and Wang, 2016).

3.2.1. Epigallocatechin-3-gallate (EGCG)

EGCG is the most abundant and active polyphenol in green tea catechin, possessing the effects of anti-cancer, anti-inflammation, anti-obesity, anti-diabetes, anti-oxidant, cardiovascular disease prevention and immunoregulation. EGCG can inhibit proliferation and induce apoptosis in many tumor cells, which is partly due to that it can epigenetically restore the expression of TSGs. It has been shown that EGCG inhibited the DNMTs activity and *DNMT1, DNMT3a* and *DNMT3b* expression, and caused CpG demethylation in promoters of silenced TSGs in acute promyelocytic leukemia cells and human skin cancer cells. Besides, EGCG inhibited the HDACs activity and increases histone H3 and H4 acetylation levels (Borutinskaite et al., 2018; Nandakumar et al., 2011).

The modulation of miRNAs by EGCG has been implicated in the cancer inhibition, anti-hypertension and protection of chronic renal injury. A recent study identified 35 up-regulated and 18 down-regulated miRNAs in hypertensive rats administrated with EGCG, among which miRNA-150–5p was indicated to be involved in the anti-hypertensive effect of EGCG (Qian et al., 2018a). EGCG increased the miRNA-15b expression in both murine and human T cells, which resulted in a significant decrease in the expression of ORAI calcium release-activated calcium modulator 1 (Orai1) and its regulator stromal cell-interaction molecule 2 (Stim2). This could inhibit the Ca^{2+} entry into murine and human T cells (Zhang et al., 2017c). In different types of cancer cells, EGCG was shown to change the expression of miRNAs (includes let-7b, miR-1, miR-21, miR-221, miR-210, miR-34a, miR-145, and miR-200c) to induce cell growth inhibition and apoptosis (Arffa et al., 2016; Devi et al., 2017; Yamada et al., 2016; Zhu and Wang, 2016).

3.2.2. Resveratrol

Resveratrol is a non-flavonoid polyphenol compound with potential therapeutic use in the treatment of human diseases, including cancer, diabetes, cardiovascular diseases (Fernandes et al., 2017). A combinatorial therapy of resveratrol and pterostilbene has been shown to be effective in treatment for estrogen receptor-alpha (ERα)-negative breast cancer, because they could decrease the expression of *DNMT*1, *DNMT3a*, *DNMT3b* and a type III HDAC enzyme *SIRT1*, decrease the DNMTs activity and 5-mC level, and increase the enrichment of H3K9 and acetyl-H4 active chromatin markers in the ERα promoter region. This eventually led to the re-activation of ERα expression and apoptosis in breast cancer cells (Kala et al., 2015; Kala and Tollefsbol, 2016). The in silico docking studies showed that resveratrol had the chemical

structure to inhibit the activity of all eleven human HDACs of class I, II and IV. In HepG2 cells, resveratrol inhibited the activity of HDACs and caused the histone hyperacetylation (Venturelli et al., 2013).

In melanoma cell lines and in vivo melanoma model, resveratrol exerted its anti-tumor effect by significantly decreasing the expression of oncogenic miR-221 and re-activating the expression of its target gene TRK-fused gene (TFG), a TSG (Wu and Cui, 2017). In a mouse model of diabetic nephropathy, resveratrol induced autophagy possibly through the suppression of miR-383–5p (Huang et al., 2017). Another study showed that resveratrol could abrogate the expression of miR-193a induced by staphylococcal enterotoxin B in the immune cells isolated from the lungs of mice, which reduced the inflammatory cytokines and as well as T cell infiltration into the lungs (Alghetaa et al., 2018). Chang et al. (2016) examined the effect of resveratrol on the myofibroblast activity of human primary fibrotic BMFs derived from oral submucous fibrosis (OSF) tissues. It was shown that resveratrol up-regulated the expression of miR-200c and the level of H3K27me3, and increased the binding of H3K27me3 to the zinc finger E-box binding homeobox 1 (*ZEB*1) promoter to inhibit the ZEB1 expression that plays a pathogenic role in the induction of myofibroblast activity and contributes to the pathogenesis of OSF.

3.2.3. Curcumin

Curcumin, a constituent of turmeric, belongs to diferuloylmethane polyphenolic compound. It has various beneficial effects such as anti-inflammatory, anti-septic, anti-oxidant, anti-cancer activities (Pandey et al., 2016). Multiple epigenetic modification potentials of curcumin have been reported so far. For example, curcumin was shown to down-regulate the protein level of DNMT1, DNMT3a, DNMT3b, HDAC1, HDAC4, and HDAC7 and the activity of DNMTs and HDACs, which caused hypomethylation and reduced the accumulation of H3k27me3 on the promoter of Nrf2 in mouse prostate cancer cells (Li et al., 2018b). Low and nontoxic concentration (10 μM) of curcumin treatment in breast cancer MCF-7 cells completely reversed the glutathione S-transferase pi 1 (*GSTPI1,* a TSG) promoter hypermethylation and re-activated its expression (Kumar et al., 2017b). Similarly, curcumin down-regulated the mRNA and protein levels of DNMT1, and re-activated the expression of tumor suppressor gene ras-association domain family protein 1A (*RASSF1A*) by decreasing its promoter methylation level in MCF-7 cells (Du et al., 2012). In human colon cancer HT29 cells, curcumin epigenetically restored the expression of TSG, deleted in lung and oesophageal cancer 1 (*DLEC1*), which was achieved by decreasing the CpG methylation in the *DLEC1* gene promoter. Furthermore, curcumin decreased the protein expression of DNMTs and HDAC4, 5, 6, and 8 (Guo et al., 2015).

Anti-cancer effect of curcumin was largely due to its regulation of microRNA expression involved in the regulation of carcinogenesis (Mirzaei et al., 2018). For example, in human colon cancer HCT-116 cells, curcumin up-regulated the anti-oncogenic miR-491 to decrease expression of paternally expressed gene-10 (PEG10) which could participate in several carcinomas (Li et al., 2018a). Curcumin treatment in several breast cancer cell lines up-regulated tumor-suppressive miRNAs (miR-181b, miR-34a, miR-16, miR-15a and miR-146b-5p) and down-regulated oncogenic miRNAs (miR-19a and miR-19b). This modulation of miRNAs led to the suppression of tumorigenesis and metastasis, and the induction of apoptosis (Norouzi et al., 2018). Curcumin promoted the radio-sensitivity in prostate cancer cells. Curcumin significantly restored the expression of miR-143 and miR-145 by reducing the expression of DNMT1 and DNMT3b and inducing promoter hypomethylation of miR-143/miR-145 cluster. MiR-143 overexpression by curcumin remarkably enhanced the radiation-induced cancer cell growth inhibition and apoptosis, and reduced the radiation-induced autophagy (Liu et al., 2017a).

3.2.4. Gallic acid

Gallic acid (GA) is a type of phenolic acid found in dietary substances like gallnuts, sumac, witch hazel, black tea and oak bark. GA possesses anti-cancer, anti-inflammatory, anti-oxidant, anti-viral and anti-bacterial properties.

It has been shown that GA strongly caused cytotoxicity against the lung cancer H1299 cells. GA reduced both nuclear and cytoplasmic levels of DNMT1 and DNMT3b, and re-activated the growth arrest and DNA damage-inducible 45 (GADD45) signaling pathway by demethylation of genes *CCNE2* (encoding cyclin E2) and *CCNB1* (encoding cyclin B1) in H1299 cells (Weng et al., 2018). Also, GA could effectively inhibit the activities of HDAC4, 5, 7, 8 and 9, but not HDAC2 and 3 (Choi et al., 2018).

The modulation of miRNA expression by GA was evaluated in several types of cancer cells. For example, in human glioblastoma cells, GA at lower dose (< 25 μg/ml) reduced, but increased at higher dose (> 50 μg/ml), the expression of miR-17–3p, miR-21–5p and miR-421–5p that are critical in regulation of antioxidant mitochondrial enzymes, cell cycle and DNA repair (Paolini et al., 2015). GA up-regulated the miR-518b in human chondrosarcoma SW1353 cells, which mediated the GA-induced apoptosis and inhibition of cell migration (Liang et al., 2014). The anti-inflammatory effects of mango polyphenols containing gallic acid were examined in rats in vivo and in normal human colon CCD-18Co cells treated with LPS. These polyphenols attenuated the expression of pro-inflammatory cytokines TNF-α, IL-1, and iNOS, and up-regulated the miR-126. The up-regulation of miR-126 further reduced its target gene PI3K (p85) and PI3K/AKT/mTOR pathway (Kim et al., 2017).

3.3. Flavonoids compounds

3.3.1. Apigenin

Apigenin is a dietary plant flavonoid present in various common fruits and vegetables (parsley, celery, chamomile tea, oranges, thyme, and onions). It possess anti-oxidant, anti-cancer, anti-inflammatory and anti-mutagenic properties (Madunic et al., 2018). The epigenetic modulatory ability of apigenin has been investigated in last decade. For example, the rats with cognitive deficits were administrated chronically with apigenin (40 mg/kg b.w. for 28 days), and showed better performance in cognitive assessment. The molecular basis is possible partly based on that apigenin treatment decreased the HDAC content, and increased the acetylated H3 and H4 expressions in the hippocampus (Tu et al., 2017). Apigenin has been shown to induce cell cycle arrest at the G2/M phase in the MDA-MB-231 breast cancer cells. Apigenin significantly inhibited the HDAC activity and induced histone H3 acetylation in the $p21^{WAF1/CIP1}$ promoter region, resulting in the increase of $p21^{WAF1/CIP1}$ transcription and cell cycle arrest (Tseng et al., 2017). Another study also showed that apigenin re-activated the crucial transcription factor Nrf2 in mouse skin epidermal JB6 P^+ cells via reversing the hypermethylated status of 15 CpG sites in the Nrf2 promoter in a dose-dependent manner. Demethylation of Nrf2 promoter accordingly increased the expression of Nrf2 and its downstream target gene NQO-1. Furthermore, apigenin treatment also reduced the expression of DNMT1, 3a and 3b, as well as HDAC1-8 (Paredes-Gonzalez et al., 2014).

It has been shown that apigenin could increase the expression of miR-520b and miR-101 in hepatocellular carcinoma cells. The overexpression of miR-520b inhibited ATG7-dependent autophagy, while overexpression of miR-101 inhibited the expression of its target gene Nrf2, both of which significantly enhanced the sensitivity of cells to doxorubicin (Gao et al., 2017, 2018a). In glioma cells, apigenin significantly increased miR-16 level, which resultantly decreased the protein expression of Bcl2 and induced apoptosis (Chen et al., 2016b).

3.3.2. Genistein and daidzein

Genistein (GE) and daidzein are the major iso-flavones (approximately 47 and 44%, respectively), that are particularly abundant in soy beans (Poschner et al., 2017). These two compounds have been widely

studied among the flavonoid group of compounds with anti-carcinogenic and anti-angiogenic activities. They also has beneficial effects such as anti-oxidant, anti-proliferation, pro-apoptosis and inhibition of tyrosine kinase (Shukla et al., 2014).

GE has been found to be a natural epigenetic modifier of DNA methylation and histone modifications. GE exposure to human cervical cancer HeLa cells significantly decreased the expression and enzymatic activity of both DNMTs and HDACs, reversed the methylation of TSGs (*MGMT, RAR-β, p21, E-cadherin, DAPK1*) in promoter region and re-activated their expression. The inhibition of DNMTs and HDACs was likely attributed to the interaction of GE with the various members of DNMT and HDAC families according to the molecular modeling analysis (Sundaram et al., 2017). In ERα-negative breast cancer cells, GE re-activated the ERα expression, which is due to that GE could lead to remodeling of chromatin structure in the *ERα* gene promoter. The ERα re-activation was synergistically enhanced by combination of GE with trichostatin A (a HDAC inhibitor). The in vivo experiments also showed that dietary GE significantly could prevent cancer development and reduce the growth of breast tumors in mice (Li et al., 2013). In MCF-7 and MDA-MB-231 breast cancer cells, daidzein, as well as GE induced demethylating and acetylating effects on histones with decrease in the H3K9me3, H3K27me3 and H3K4me3 levels, and increase in acetylation level of H4K8 and H3K4. This in turn led to the unpacking of chromatin and the transcription enhancement (Dagdemir et al., 2013).

3.3.3. Quercetin

Quercetin belongs to the flavonoids and is abundant in many fruits and vegetables (broccoli, onions, dill, cilantro, citrus fruits and buckwheat). It was reported that quercetin prevented high fat diet-induced hypermethylation in the peroxisome proliferator activated-receptor gamma co-activator 1 alpha (*PGC-1α*) promoter, which re-activated the expression of PGC-1α and ameliorated high fat diet-induced obesity and insulin resistance (Devarshi et al., 2017). Quercetin alone or with curcumin treatment could inhibit the DNMTs activity, and caused global hypomethylation and increased androgen receptor (AR) mRNA and protein levels in AR-negative prostate cancer cells, indicating their potential for chemoprevention of androgen resistance in prostate cancer (Sharma et al., 2016). In hamster buccal pouch tumor model, quercetin was shown to reduce tumor incidence, induce cell cycle arrest or apoptosis, and block invasion and angiogenesis. Meanwhile, a positive correlation between the inhibition of HDAC1 and DNMT1 by quercetin and its anti-cancer properties was revealed (Priyadarsini et al., 2011). In human leukemia HL-60 cells, quercetin induced apoptosis which was partly through the induction of Fas ligand (FasL). Quercetin exhibited the potential to activate HAT and inhibit HDAC, both of which contributed to histone H3 acetylation in *FasL* gene (Lee et al., 2011).

Quercetin exerted its anti-cancer stem cells (CSCs) in human pancreatic ductal adenocarcinoma (PDA) cells and primary human PDA cells. The small subpopulation of CSCs endow the tumor tissue with pronounced therapy resistance and early progression of PDA. Quercetin was shown to inhibit the viability, migratory potential and induce the apoptosis of CSCs, and mediated the overexpression of miR-let-7a that in turn reduce the K-ras expression and CSC features in pancreatic cancer (Appari et al., 2014). Oncogenic miR-21 has been involved in chronic Cr exposure-induced malignant transformation of human bronchial epithelial cells through inhibition of the tumor suppressor gene *PDCD4* (encoding programmed cell death 4). The quercetin treatment abrogated the miR-21 expression and reversed the inhibition of PDCD4 and malignant transformation of cells (Pratheeshkumar et al., 2017).

3.4. Cruciferous vegetables

Several epidemiological investigations have shown a strong correlation between lower incidence of cancers in lung, breast, gastric, bladder, colorectal, pancreatic, prostate, and kidney with a higher and long-term intake of cruciferous vegetables (Abbaoui et al., 2017; Johnson, 2018; Veeranki et al., 2015). The anti-cancer activity of cruciferous vegetables mainly comes from the bioactive compounds sulforaphane (SFN) and phenethyl isothiocyanate (PEITC), of which PEITC represents the most potent and promising one in preventing the cancer development and progression (Veeranki et al., 2015).

3.4.1. Sulforaphane (SFN)

SFN is an isothiocyanate abound in broccoli, broccoli sprouts and Brussels sprouts, and has been characterized as HDAC inhibitor. In the study of Choi et al. (2018), the inhibitory effect of HDAC activity by SFN was analyzed in cell free system, and the results showed that SFN (> 100 μM) mildly decreased the activities of HDAC4, 5, and 7, but strongly decreased the HDAC9 and 2 activities. A combinatorial treatment of physiologically achievable concentrations of SFN and withaferin A (WA), a steroidal lactone derived from Indian winter cherry, in human breast cancer cells resulted in a decrease in the expression of DNMT1, 3a and 3b and HDAC1, and inhibition in DNMT and HDAC activities. This treatment also synergistically inhibited the cellular viability, and promoted the apoptosis in breast cancer cells (Royston et al., 2017). SFN has been suggested to exert its chemopreventive and anti-oxidant activities via the activation of Nrf2 (Russo et al., 2018). It was shown that SFN treatment in prostate cancer TRAMP C1 cells attenuated the expression of HDAC1, 4, 5, and 7, increased the acetylation level of histone 3, and led to demethylation of the first 5 CpGs in the promoter region of Nrf2. This could restore the expression of Nrf2 and its target gene NQO-1 (Li et al., 2018b; Zhang et al., 2013).

SFN could restore the miR-9-3 level in lung cancer A549 cells through epigenetic regulation. SFN treatment attenuated the DNMT activity and the expression of DNMT3a and HDAC1, 3 and 6, which reduced the CpG methylation and increased the transcriptional activity of miR-9-3 promoter (Gao et al., 2018b). In colorectal cancer cells, SFN down-regulated the expression of miR-21 and HDAC1, which resulted in decreased expression of human telomerase reverse transcriptase (hTERT) that is essential for continued proliferation. SFN reduced telomerase protein and its enzymatic activity, and eventually led to inhibition of cell viability and induction of apoptosis (Martin et al., 2018).

3.4.2. Phenethyl isothiocyanate (PEITC)

PEITC is another isothiocyanate, whose precursor gluconasturtiin is found in cruciferous vegetables watercress. PEITC can modulate the phase I drug metabolizing enzymes and phase II detoxification enzymes to affect the bio-activation and the detoxifying process of carcinogens (Osman et al., 2017). Emerging evidences also showed that PEITC had chemopreventive property against cancers through epigenetic mechanisms including DNA methylation, histone modification and miRNAs expression.

In a recent study, it has been reported that long-term exposure (> 1 month) of colorectal cancer SW620 cells to low-dose PEITC could alter the expression profile of epigenetic writers/erasers. This therapy not only blocked HDAC binding to euchromatin, but also induced hypomethylation of polycomb-group (PcG) target genes that are typically hypermethylated in cancers. As a result, PEITC inhibited the proliferation of colorectal cancer cells and growth of SW620-derived tumors in a mouse xenograft model (Park et al., 2017). In human prostate adenocarcinoma cells LNCaP, PEITC decreased the protein expression of DNMT1, 3a and 3b and HDAC1, 2, 4 and 6, and significantly enhanced the CpG demethylation in *RASSF1A* promoter and accordingly re-activated its expression. This could promote the early apoptosis and G2/M cell cycle arrest in this cancer cells (Boyanapalli et al., 2016).

PEITC may exert its anti-cancer effect through modulation of multiple miRNAs. In LNCaP cells, PEITC increased the expression of anti-oncogenic miRNA-194 which interacted with its direct target bone morphogenetic protein 1 (*BMP1*). The down-regulation of BMP1 decreased the expression of key oncogenic matrix metalloproteinases MMP2 and MMP9, which in turn inhibited cancer cell invasion (Zhang

Table 5
Potential epigenetic nutrition and their actions on DNMTs, HDACs and miRNAs.

Compounds	Major sources	Actions on DNMTs	Actions on HDACs	Actions on miRNAs	References
Folic acid and vitamin B12	Kiwis, oats, aloes, broccoli, carrot	Acts as methyl donor to support the methylation. Increases DNMT expression, and DNMT activity.			(Liu et al., 2016b; Sanchez et al., 2017)
Epigallocatechin-3-gallate (EGCG)	Green tea, white tea, black tea	Decreases DNMT and HDAC activity, Downregulates DNMT and re-activates TSGs expression in cancer cells.	Decrease chromatin binding of p65 with histone acetyltransferase p300, as well as increase chromatin binding of HDAC 1/2, induce hypoacetylation of H3 in human endothelial cells. Significantly reduce the enhancer of zeste homolog 2 (EZH2) and class I HDAC protein levels in breast cancer cells.	Up-regulates miR-1 in osteosarcoma cells. Down-regulates oncogenic miR-21 and up-regulates tumor suppressor miR-330 in prostate cancer cells. Up-regulates miR-210 in lung cancer cells. Up-regulates miR-34a, miR-145, and miR-200c to enhance chemosensitivity in colorectal cancer cells.	(Deb et al., 2015; Khan et al., 2015; Liu et al., 2016a; Toden et al., 2016; Wang et al., 2011; Zhang et al., 2017c; Zhu and Wang, 2016)
Genistein	Soybeans	Decreases global DNA methylation, DNMT activity and DNMT1 expression in breast cancer cells. Inhibits DNMT3b expression, decreases hypermethylation of TSG CHD5 and p53 in neuroblastoma.	Increases histones H3 and H4 acetylation and HAT activity, decreases HDAC6 and SIRT1 expression in prostate cancer cells. Re-activates ER-α expression in ER-α-negative breast cancer cells.	Restores miR-574–3p expression in prostate cancer cells to induce apoptosis. Reduces miR-21 level in renal cancer cells. Inhibits oncogenic miR-95 and its targets Akt in colon cancer cells. Inhibits miR-145 in retinoblastoma cells. Inhibits miR-155 in metastatic breast cancer cells.	(Chiyomaru et al., 2013; de la Parra et al., 2016; Kikuno et al., 2017; Li et al., 2012, 2013; Qin et al., 2015; Roh et al., 2004; Sundaram et al., 2017; Wei et al., 2017; Zaman et al., 2012)
Daidzein	Soybeans	Causes demethylation of glutathione S-transferase P1 and ephrin B2 promoter regions and re-activates their expression in human prostate cancer cells.		Downregulates oncogenic miR-125b, miR-155, miR-211, miR-367a, and miR-320, and upregulates tumor-suppressor miR-15a in human prostate cancer cells.	(Adjakly et al., 2011, 2015)
Curcumin	Turmeric	Inhibits DNMT1 and 3b in prostate cancer cells. Inhibits DNMT1, 3a, and 3b in invasive ductal breast carcinoma. Reduces binding of p65 and Sp1 to DNMT1 promoter and decreases DNMT1 expression, reactivates $p15^{INK4B}$, induces G1 cell cycle arrest and apoptosis in AML.	Increases HDAC1, 4, 5, 8 expression, but decreases HDAC3 expression. Decreases H3K27me3 level in human prostate cancer cells. Decreases HDAC1 protein level in invasive ductal breast carcinoma. inhibits HDAC activity.	Increases miR-378 to inhibit glioblastoma growth. Decreases miR-130a to inhibit colon cancer cell proliferation. Up-regulates miR-98 to suppress lung cancer cell migration and invasion.	(Dou et al., 2017; Li et al., 2017; Liu et al., 2017a, 2017b; Mirza et al., 2013; Norouzi et al., 2018; Shu et al., 2011; Yu et al., 2013b)
Sulforaphane	Broccoli, broccoli sprouts and Brussels sprouts	Reduces DNMT1 expression in porcine satellite cells. Causes global hypo-methylation and downregulation of DNMT1 and 3b in prostate cancer cells and breast cancer cells. Reactivates cyclin D2 by demethylation in its promoter in prostate cancer cells.	Decreases expression of HDAC1, 4, 5, and 7 in prostate cancer cells. Inhibits the activity of HDAC1, 2, 4 and 6, decreases histone H1 phosphorylation in human bladder cancer cells. Inhibits HDAC activity and increases acetylated histones H3 and H4 in lung cancer cells.	Decrease the levels of miR-23b, miR-92b, miR-381 and miR-382 in breast cancer cells. Downregulates oncogenic miR-21 in colorectal cancer cells.	(Abbaoui et al., 2017; Hsu et al., 2011; Jiang et al., 2016; Lewinska et al., 2017; Li et al., 2018b; Lubecka-Pietruszewska et al., 2015; Martin et al., 2018; Zhang et al., 2013)
Quercetin	broccoli, onions, dill, cilantro, citrus fruits and buckwheat	Inhibits DNMT1 and HDAC1 and blocks invasion and angiogenesis in hamster buccal pouch tumors. Inhibits class I HDAC in leukemia. Inhibits DNMT1 and 3a, and induces apoptosis in gastric carcinoma cells.	Inhibits SIRT6. Induces histone hyperacetylation and increases histone acetylation in human leukemia cells. Activates HAT and inhibits HADC, leading to histone H3 acetylation in human leukemia cells.	Decreases oncogenic miR-27a and increases zinc finger protein ZBTB10 to reduce specificity protein (Sp) transcription factors required for cell proliferation.	(Appari et al., 2014; Jia and Chen, 2008; Lee et al., 2011, 2015; Li et al., 2014; Priyadarsini et al., 2011; Trevino-Saldana and Garcia-Rivas, 2017)
Apigenin	parsley, celery, chamomile tea, oranges, thyme	Reduces DNMT1, 3a, and 3b expression, reverses the hypermethylated status of 15 CpG sites in the Nrf2 promoter and re-activates Nrf2 expression in mouse skin epidermal JB6 P + cells.	Inhibits HDAC activity and specifically HDAC1 and HDAC3 expression, induces histone H3 and H4 acetylation on the $p21^{WAF1/CIP1}$ promoter in human prostate cancer cells.	Decrease the expression levels of mature miR122 in human liver cancer cells Huh-7 to inhibit hepatitis C virus replication. Suppress matured miR103 expression levels in mice.	(Ohno et al., 2013; Pandey et al., 2012; Paredes-Gonzalez et al., 2014; Shibata et al., 2014; Tseng et al., 2017)
Resveratrol	Grapes, blueberries, raspberries, mulberries	Decreases DNMT1, and 3b expression in mammary tumors. Demethylates RASSF1A by inhibiting DNMTs activity in breast cancer cells. Decreases DNMT1, DNMT3a and DNMT3b expression in breast cancer cells.	Inhibits SIRT1 expression to induce cell cycle arrest in triple-negative breast cancer cells. Resveratrol inhibit all eleven human HDACs of class I, II and IV in human-derived hepatoblastoma cells.	Inhibits oncogenic miR-17, miR-20a, miR-106a, miR-106b in prostate cancer cells. Inhibits miR-21 in bladder cancer cells and pancreatic cancer cells. Inhibits miR-196b and miR-1290 in AML. Inhibits oncogenic miR-21, miR-30a-5p and miR-19 in glioma cells.	(Dhar et al., 2015; Kala et al., 2015; Lee et al., 2018; Mirza et al., 2013; Qin et al., 2014; Venturelli et al., 2013; Wang et al., 2015; Wu and Cui, 2017; Zhou et al., 2014a, 2017)

(*continued on next page*)

Table 5 (*continued*)

Compounds	Major sources	Actions on DNMTs	Actions on HDACs	Actions on miRNAs	References
Pterostilbene	Grape, blueberries, almonds, vaccinium berries	Combinatorial resveratrol and pterostilbene decreases DNMT activity and 5-methylcytosine level in breast cancer cells.	Increases the enrichment of acetyl-H3, acetyl-H3lysine9 and acetyl-H4 in ER alpha promoter and reactivate ER alpha expression in breast cancer cells.	Downregulates miR-19a, which increases phosphatase and tensin homolog (PTEN) expression, leading to cell cycle arrest and apoptosis in hepatocellular carcinoma.	(Kala and Tollefsbol, 2016; Qian et al., 2018b)
Gallic acid	Gallnuts, sumac, witch hazel, tea leaves, oak bark	Reduces both nuclear and cytoplasmic DNMT1 and 3b in human lung cancer cells. Restores the depletion of DNMT1 to protect against endothelial injury in human vascular endothelial cells.	Remarkable inhibits class IIa (HDAC4, 5, 7, 9) HDAC activities, weakly inhibits HDAC1 and 6 activities, but strongly inhibits HDAC8 activity in the cell-free system.	Changes the expression of miR-17–3p, miR-21–5p and miR-421–5p to inhibit the tumor growth and invasion in human glioblastoma cells.	(Choi et al., 2018; Kam et al., 2014; Paolini et al., 2015; Weng et al., 2018)
Phenethyl isothiocyanate (PEITC)	Watercress	Reduces DNMT1, 3a and 3b expression, decreases RASSFIA promoter methylation and re-activates RASSFIA and GSTP1 expression, leading to apoptosis in prostate cancer cells.	Inhibits HDAC1, 2, 4 and 6, increases histone H3K4 acetylation in prostate cancer cells. Low-dose PEITC exposure blocks HDAC binding to euchromatin in colon cancer cells.	Upregulates miR-194 which inhibits oncogenic MMP2 and MMP9 and cell invasion in prostate cancer cells.	(Boyanapalli et al., 2016; Izzotti et al., 2010; Park et al., 2017; Zhang et al., 2016)
Peperomin E	Peperomia dindygulensis	Decreases DNMT1 expression and global methylation, reactivates RASSF1A, APC, RUNX3, and $p16^{INK4}$.			Wang et al. (2016a)
Emodin	Rhubarb, buckthorn, fungi metabolites	Decreases DNMT1 and 3a expression and increases expression of TSGs p16, RASSF1A and ppENK.	Decreases HDAC activity and HDAC1 expression to inhibit pro-inflammatory responses in hypoxic rheumatoid synoviocytes.	Activates miR-199a which inhibits expression of TGF-2 in human ovarian carcinoma cells. Increases miR-221 and miR-222 to induce human myelogenous leukemia erythroid differentiation.	(Ha et al., 2011; Ma et al., 2013; Pan et al., 2016; Song et al., 2018)
Mahanine	Micromelum minutum	Induces the degradation of DNMT1 and DNMT 3b, but not DNMT3a, induces demethylation of RASSF1A promoter in prostate cancer cells.			Agarwal et al. (2013)
Dioscin	Saponin	Increases mRNA level of DNMT3a in human breast cancer cells.	Upregulates Sirt3 to decrease oxidative stress. Activates Nrf2 and Sirt2 to combat the oxidative stress in rat cardiomyocytes.	Decrease miR-140–5p level to affect the expression levels of oxidative stress-related genes of HO-1, NQO1, Gst, GCLM, Keap1 and FOXO3a.	(Aumsuwan et al., 2016; Qiao et al., 2018)
Patchouli alcohol	Pogostemonis Herba		Inhibits HDAC2 and c-myc, and HDAC activity, increases p21 eepression, decreases the expressions of cyclin D1 and CDK4, and induces apoptosis in human colorectal cancer cells.		Jeong et al. (2013)
Kaempferol	Tea, broccoli, cabbage, kale, beans, endive, leek, tomato, strawberries and grapes		Fits into the binding pocket of HDAC2, 4, 7 or 8, thereby binds to the zinc ion of the catalytic center, inhibits activity of all class I, II and IV HDACs. Induces hyperacetylation of histone H3 in human colon cancer cells and hepatoma cells.		Berger et al. (2013)
Chrysin	Honey, propolis, chamomile, mushroom		Inhibits HDAC8 activity, suppress cell growth and induce differentiation in breast cancer cells.		Sun et al. (2012)
Diallyl disulfide	Garlic		Inhibits HDAC activity, increases histone H3 and H4 acetylation in human colon tumor cells.		(Druesne et al., 2004; Wallace et al., 2013)
Ginsenoside-Rh2	Ginseng		Downregulates HDAC1, 2, and 6, increases histone H3 acetylation and HAT activity in human leukemia cells.		Liu et al. (2015)

et al., 2016). PEITC also increased the expression of anti-oncogenic miRNA-17, which resulted in a decrease in p300/CBP-associated factor (PCAF) expression and growth inhibition in LNCaP cells (Yu et al., 2013a). Izzotti et al. (2010) evaluated the expression of 576 miRNAs in the liver and lung of neonatal mice exposed to environmental cigarette smoke (ECS) for 2 weeks. Of which 72 and 166 miRNAs were dysregulated in the lung and liver, respectively. However, the treatment with the diet containing PEITC protected the lung and liver from ECS-induced alterations of miRNAs expression.

3.5. Organosulfur compounds (OSCs)

OSCs are mostly derived from Allium family vegetables such as onion, garlic and shallots. They have been historically used as benefits for health improvements in the folk due to their advantages in cancer prevention, anti-microbial activity, improved immunity, hypoglycemic activity and promotion of cardiovascular health (Petropoulos et al., 2017). The diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS) and the active metabolite S-allylmercaptocysteine (SAMC) of DADS are the major active ingredients of OSCs (Petropoulos et al., 2017), and the DADS and DATS are more studied and thus get more attention.

3.5.1. Diallyl disulfide (DADS) and diallyl trisulfide (DATS)

It has been reported that DADS could inhibit the proliferation of different types of cancer cells and growth of tumors in experimental animals. The anti-tumor effect of DADS was derived from multiple mechanisms, including activation of metabolizing enzymes that detoxify carcinogens, anti-oxidant activity, induction of cell cycle arrest and apoptosis, inhibition in angiogenesis and invasion, and histone modification (Yi and Su, 2013).

DADS can lower the incidence of breast cancer both in vitro and in vivo. Studies have suggested that DADS could induce the apoptosis in the breast cancer MCF-7 cells. Also, DADS decreased the histone deacetylation process and induced hyperacetylation in histone H4 in a way similar to HDACi (Altonsy et al., 2012). In colon cancer cells Caco-2 and HT-29, DADS inhibited the HDAC activity, and induced histone H3 and H4 hyperacetylation preferentially at H4K12 and H4K16. This partly

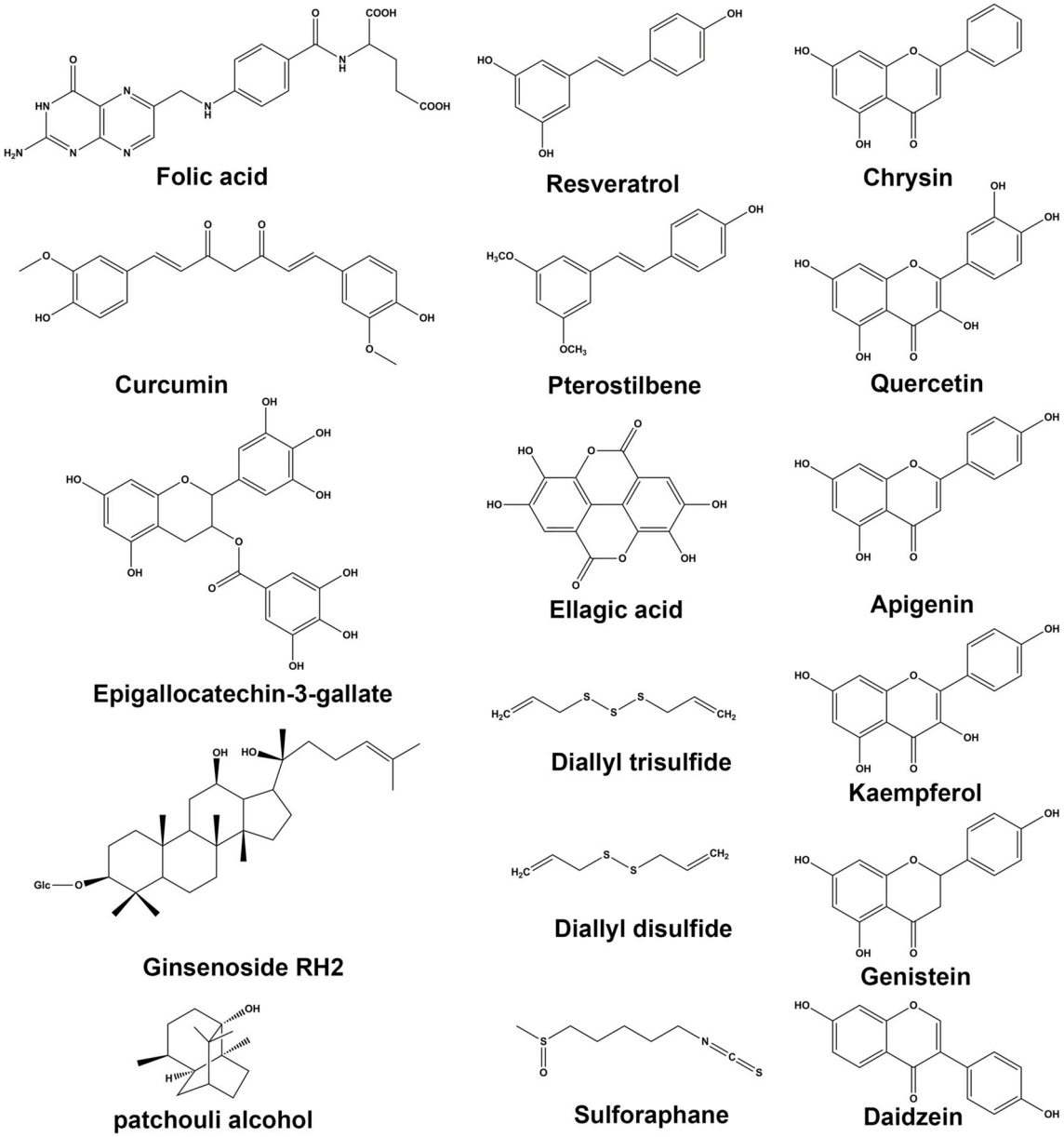

Fig. 3. The chemical structures of compounds from natural epigenetic nutritions.

resulted in an increase in p21 $^{WAF1/CIP1}$ expression and cell cycle arrest (Druesne et al., 2004).

DATS has been shown to inhibit the HDAC activity and impede glioblastoma tumor progression in ectopic glioblastoma xenograft mice model. DATS increased the acetylation level of H3 and H4, inhibited the cell cycle progression, and reduced the tumor mass and numbers of mitotic cells within tumors (Wallace et al., 2013). The potential epigenetic nutrition and their actions are listed in Table 5. The chemical structures of these epigenetic nutrition are shown in Fig. 3.

4. Conclusion and future perspectives

Based on the emerging regulatory role of aberrant epigenetic modifications in the etiology of various human diseases and the pathological conditions in a variety of cells, it is possible and necessary to develop the therapeutic agent to restore these epigenetic abnormalities. DNA methylation, histone modification and miRNAs expression mostly represent the research direction of epigenetics. It has been indicated that DNMTs and HDACs reveal a reduced expression level in certain types of cancer. Also, an aberrant miRNAs expression pattern is common in cancer cells. The therapeutics targeting the DNMTs, HDACs and miRNAs hold great promises in the treatment of various cancers and other human diseases. Meanwhile, the new discipline termed as “epigenetic therapy” has arisen, and many epigenetic agents, including DNMTs and HDACs inhibitors are in the pre-clinical and clinical trial phases. However, a key challenge for the epigenetic therapy is to develop the inhibitors of DNMTs and HDACs with higher DNA specificity, thereby reducing the side effects.

So far, there are still few epigenetic drugs that were approved by the authorities to treat the human diseases. Perhaps, the research focus should move on to discover the active naturally occurring epigenetic nutrition. A numbers of evidences have shown that the epigenetic nutrition have the potential to modulate the epigenetic states, thus it could be considered as a potential alternative for epigenetic therapy. Furthermore, it has been suggested that the combinations of epigenetic nutrition-derived compounds may achieve a better effect than used alone. Thus, the combined effectiveness of different epigenetic nutrition probably should be explored. Moreover, the guidelines for sufficient daily intake of nutrition, prevention of nutritional deficiencies and a different combinations of nutrition may also be needed.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (grant no. 31572575), the Fundamental Research Funds for the Central Universities (2662016PY115).

References

Anonymous, 2009. US FDA recommendation for romidepsin in cutaneous T-cell lymphoma. Expert Rev Anticanc 9 1546-1546.
Abbaoui, B., Telu, K.H., Lucas, C.R., Thomas-Ahner, J.M., Schwartz, S.J., Clinton, S.K., Freitas, M.A., Mortazavi, A., 2017. The impact of cruciferous vegetable isothiocyanates on histone acetylation and histone phosphorylation in bladder cancer. J Proteomics 156, 94–103.
Adjakly, M., Bosviel, R., Rabiau, N., Boiteux, J.P., Bignon, Y.J., Guy, L., Bernard-Gallon, D., 2011. DNA methylation and soy phytoestrogens: quantitative study in DU-145 and PC-3 human prostate cancer cell lines. Epigenomics-Uk 3, 795–803.
Adjakly, M., Ngollo, M., Dagdemir, A., Judes, G., Pajon, A., Karsli-Ceppioglu, S., Penault-Llorca, F., Boiteux, J.P., Bignon, Y.J., Guy, L., Bernard-Gallon, D., 2015. Prostate cancer: the main risk and protective factors - epigenetic modifications. Ann Endocrinol-Paris 76, 25–41.
Agarwal, S., Amin, K.S., Jagadeesh, S., Baishay, G., Rao, P.G., Barua, N.C., Bhattacharya, S., Banerjee, P.P., 2013. Mahanine restores RASSF1A expression by down-regulating DNMT1 and DNMT3B in prostate cancer cells. Mol. Canc. 12.
Ahn, M.-Y., Ahn, J.-W., Kim, H.-S., Lee, J., Yoon, J.-H., 2015. Apicidin inhibits cell growth by downregulating IGF-1R in salivary mucoepidermoid carcinoma cells. Oncol. Rep. 33, 1899–1907.
Ahn, M.Y., Kang, D.O., Na, Y.J., Yoon, S., Choi, W.S., Kang, K.W., Chung, H.Y., Jung, J.H., Min, D.S., Kim, H.S., 2012. Histone deacetylase inhibitor, apicidin, inhibits human ovarian cancer cell migration via class II histone deacetylase 4 silencing. Cancer Lett. 325, 189–199.
Aldawsari, F.S., Aguayo-Ortiz, R., Kapilashrami, K., Yoo, J., Luo, M.K., Medina-Franco, J.L., Velazquez-Martinez, C.A., 2016. Resveratrol-salicylate derivatives as selective DNMT3 inhibitors and anticancer agents. J. Enzym. Inhib. Med. Chem. 31, 695–703.
Alghetaa, H., Mohammed, A., Sultan, M., Busbee, P., Murphy, A., Chatterjee, S., Nagarkatti, M., Nagarkatti, P., 2018. Resveratrol protects mice against SEB-induced acute lung injury and mortality by miR-193a modulation that targets TGF-beta signalling. J. Cell Mol. Med. 22, 2644–2655.
Altonsy, M.O., Habib, T.N., Andrews, S.C., 2012. Diallyl disulfide-induced apoptosis in a breast-cancer cell line (MCF-7) may Be caused by inhibition of histone deacetylation. Nutr. Canc. 64, 1251–1260.
Amato, R.J., Stephenson, J., Hotte, S., Nemunaitis, J., Belanger, K., Reid, G., Martell, R.E., 2012. MG98, a second-generation DNMT1 inhibitor, in the treatment of advanced renal cell carcinoma. Canc. Invest. 30, 415–421.
Andrade, A.F., Borges, K.S., Suazo, V.K., Geron, L., Correa, C.A.P., Castro-Gamero, A.M., de Vasconcelos, E.J.R., de Oliveira, R.S., Neder, L., Yunes, J.A., Aguiar, S.D., Scrideli, C.A., Tone, L.G., 2017. The DNA methyltransferase inhibitor zebularine exerts antitumor effects and reveals BATF2 as a poor prognostic marker for childhood medulloblastoma. Invest. N. Drugs 35, 26–36.
Appari, M., Babu, K.R., Kaczorowski, A., Gross, W., Herr, I., 2014. Sulforaphane, quercetin and catechins complement each other in elimination of advanced pancreatic cancer by miR-let-7 induction and K-ras inhibition. Int. J. Oncol. 45, 1391–1400.
Aranda, J., Attana, F., Tunon, I., 2017. Molecular mechanism of inhibition of DNA methylation by zebularine. ACS Catal. 7, 1728–1732.
Arffa, M.L., Zapf, M.A., Kothari, A.N., Chang, V., Gupta, G.N., Ding, X., Al-Gayyar, M.M., Syn, W., Elsherbiny, N.M., Kuo, P.C., Mi, Z., 2016. Epigallocatechin-3-Gallate upregulates miR-221 to inhibit osteopontin-dependent hepatic fibrosis. PloS One 11, 18.
Aumsuwan, P., Khan, S.I., Khan, I.A., Ali, Z., Avula, B., Walker, L.A., Shariat-Madar, Z., Helferich, W.G., Katzenellenbogen, B.S., Dasmahapatra, A.K., 2016. The anticancer potential of steroidal saponin, dioscin, isolated from wild yam (Dioscorea villosa) root extract in invasive human breast cancer cell line MDA-MB-231 in vitro. Arch. Biochem. Biophys. 591, 98–110.
Azad, N.S., el-Khoueiry, A., Yin, J., Oberg, A.L., Flynn, P., Adkins, D., Sharma, A., Weisenberger, D.J., Brown, T., Medvari, P., Jones, P.A., Easwaran, H., Kamel, I., Bahary, N., Kim, G., Picus, J., Pitot, H.C., Erlichman, C., Donehower, R., Shen, H., Laird, P.W., Piekarz, R., Baylin, S., Ahuja, N., 2017. Combination epigenetic therapy in metastatic colorectal cancer (mCRC) with subcutaneous 5-azacitidine and entinostat; a phase 2 consortium/stand up 2 cancer study. Oncotarget 8, 35326–35338.
Bak, R.O., Mikkelsen, J.G., 2014. miRNA Sponges: Soaking up miRNAS for Regulation of Gene Expression 5. Wiley Interdisciplinary Reviews-Rna, pp. 317–333.
Balasubramaniam, S., Redon, C.E., Peer, C.J., Bryla, C., Lee, M.-J., Trepel, J.B., Tomita, Y., Rajan, A., Giaccone, G., Bonner, W.M., Figg, W.D., Fojo, T., Piekarz, R.L., Bates, S.E., 2018. Phase I trial of belinostat with cisplatin and etoposide in advanced solid tumors, with a focus on neuroendocrine and small cell cancers of the lung. Anti Canccer Drugs 29, 457–465.
Ball, B., Zeidan, A., Gore, S.D., Prebet, T., 2017. Hypomethylating agent combination strategies in myelodysplastic syndromes: hopes and shortcomings. Leuk. Lymphoma 58, 1022–1036.
Banerji, U., van Doorn, L., Papadatos-Pastos, D., Kristeleit, R., Debnam, P., Tall, M., Stewart, A., Raynaud, F., Garrett, M.D., Toal, M., Hooftman, L., De Bono, J.S., Verweij, J., Eskens, F.A.L.M., 2012. A phase I pharmacokinetic and pharmacodynamic study of CHR-3996, an oral class I selective histone deacetylase inhibitor in refractory solid tumors. Clin. Canc. Res. 18, 2687–2694.
Beg, M.S., Brenner, A.J., Sachdev, J., Borad, M., Kang, Y.-K., Stoudemire, J., Smith, S., Bader, A.G., Kim, S., Hong, D.S., 2017. Phase I study of MRX34, a liposomal miR-34a mimic, administered twice weekly in patients with advanced solid tumors. Invest. N. Drugs 35, 180–188.
Berger, A., Venturelli, S., Kallnischkies, M., Bocker, A., Busch, C., Weiland, T., Noor, S., Leischner, C., Weiss, T.S., Lauer, U.M., Bischoff, S.C., Bitzer, M., 2013. Kaempferol, a new nutrition-derived pan-inhibitor of human histone deacetylases. J. Nutr. Biochem. 24, 977–985.
Berger, S.L., Kouzarides, T., Shiekhattar, R., Shilatifard, A., 2009. An operational definition of epigenetics. Gene Dev. 23, 781–783.
Bitzer, M., Horger, M., Giannini, E.G., Ganten, T.M., Woerns, M.A., Siveke, J.T., Dollinger, M.M., Gerken, G., Scheulen, M.E., Wege, H., Zagonel, V., Cillo, U., Trevisani, F., Santoro, A., Montesarchio, V., Malek, N.P., Holzapfel, J., Herz, T., Ammendola, A.S., Pegoraro, S., Hauns, B., Mais, A., Lauer, U.M., Henning, S.W., Hentsch, B., 2016. Resminostat plus sorafenib as second-line therapy of advanced hepatocellular carcinoma - the SHELTER study. J. Hepatol. 65, 280–288.
Borutinskaite, V., Virksaite, A., Gudelyte, G., Navakauskiene, R., 2018. Green tea polyphenol EGCG causes anti-cancerous epigenetic modulations in acute promyelocytic leukemia cells. Leuk. Lymphoma 59, 469–478.
Boyanapalli, S.S.S., Li, W., Fuentes, F., Guo, Y., Ramirez, C.N., Gonzalez, X.P., Pung, D., Kong, A.N.T., 2016. Epigenetic reactivation of RASSF1A by phenethyl isothiocyanate (PEITC) and promotion of apoptosis in LNCaP cells. Pharmacol. Res. 114, 175–184.
Brueckner, B., Rius, M., Markelova, M.R., Fichtner, I., Hals, P.A., Sandvold, M.L., Lyko, F., 2010. Delivery of 5-azacytidine to human cancer cells by elaidic acid esterification increases therapeutic drug efficacy. Mol. Canc. Therapeut. 9, 1256–1264.
Butler, L.M., Webb, Y., Agus, D.B., Higgins, B., Tolentino, T.R., Kutko, M.C., LaQuaglia, M.P., Drobnjak, M., Cordon-Cardo, C., Scher, H.I., Breslow, R., Richon, V.M., Rifkind,

R.A., Marks, P.A., 2001. Inhibition of transformed cell growth and induction of cellular differentiation by pyroxamide, an inhibitor of histone deacetylase. Clin. Canc. Res. 7, 962–970.
Byun, H.-M., Choi, S.H., Laird, P.W., Trinh, B., Siddiqui, M.A., Marquez, V.E., Yang, A.S., 2008. 2 '-deoxy-N4- 2-(4-nitrophenyl)ethoxycarbonyl -5-azacytidine: a novel inhibitor of DNA methyltransferase that requires activation by human carboxylesterase. Cancer Lett. 266, 238–248.
Campbell, P., Thomas, C.M., 2017. Belinostat for the treatment of relapsed or refractory peripheral T-cell lymphoma. J. Oncol. Pharm. Pract. 23, 143–147.
Caulfield, T., Medina-Franco, J.L., 2011. Molecular dynamics simulations of human DNA methyltransferase 3B with selective inhibitor nanaomycin A. J. Struct. Biol. 176, 185–191.
Ceballos, M.P., Decandido, G., Quiroga, A.D., Comanzo, C.G., Livore, V.I., Lorenzetti, F., Lambertucci, F., Chazarreta-Cifre, L., Banchio, C., Alvarez, M.D., Mottino, A.D., Carrillo, M.C., 2018. Inhibition of sirtuins 1 and 2 impairs cell survival and migration and modulates the expression of P-glycoprotein and MRP3 in hepatocellular carcinoma cell lines. Toxicol. Lett. 289, 63–74.
Chan, E., Chiorean, E.G., O'Dwyer, P.J., Gabrail, N.Y., Alcindor, T., Potvin, D., Chao, R., Hurwitz, H., 2018. Phase I/II study of mocetinostat in combination with gemcitabine for patients with advanced pancreatic cancer and other advanced solid tumors. Cancer Chemother. Pharmacol. 81, 355–364.
Chang, Y.-C., Lin, C.-W., Yu, C.-C., Wang, B.-Y., Huang, Y.-H., Hsieh, Y.-C., Kuo, Y.-L., Chang, W.-W., 2016. Resveratrol suppresses myofibroblast activity of human buccal mucosal fibroblasts through the epigenetic inhibition of ZEB1 expression. Oncotarget 7, 12137–12149.
Cheishvili, D., Boureau, L., Szyf, M., 2015. DNA demethylation and invasive cancer: implications for therapeutics. Br. J. Pharmacol. 172, 2705–2715.
Chen, A.C., Martin, A.J., Dalziell, R.A., McKenzie, C.A., Lowe, P.M., Eris, J.M., Scolyer, R.A., Dhillon, H.M., Vardy, J.L., Bielski, V.A., Halliday, G.M., Damian, D.L., 2016a. A phase II randomized controlled trial of nicotinamide for skin cancer chemoprevention in renal transplant recipients. Br. J. Dermatol. 175, 1073–1075.
Chen, L.Y., Jin, T.F., Zhu, K., Piao, Y.S., Quan, T.H., Quan, C.J., Lin, Z.H., 2017a. PI3K/mTOR dual inhibitor BEZ235 and histone deacetylase inhibitor Trichostatin A synergistically exert anti-tumor activity in breast cancer. Oncotarget 8, 11937–11949.
Chen, X.J., Wu, M.Y., Li, D.H., You, J., 2016b. Apigenin inhibits glioma cell growth through promoting microRNA-16 and suppression of BCL-2 and nuclear factor-B/MMP-9. Mol. Med. Rep. 14, 2352–2358.
Chen, Y.J., Wan, W.H., Wu, W.Y., Hsu, C.C., Wei, L.R., Wang, S.F., Hsu, Y.W., Liaw, C.C., Tsai, W.C., 2017b. Novel histone deacetylase inhibitor AR-42 exhibits antitumor activity in pancreatic cancer cells by affecting multiple biochemical pathways. PloS One 12, 18.
Child, F., Ortiz-Romero, P.L., Alvarez, R., Bagot, M., Stadler, R., Weichenthal, M., Alves, R., Quaglino, P., Beylot-Barry, M., Cowan, R., Geskin, L.J., Perez-Ferriols, A., Hellemans, P., Elsayed, Y., Phelps, C., Forslund, A., Kamida, M., Zinzani, P.L., 2016. Phase II multicentre trial of oral quisinostat, a histone deacetylase inhibitor, in patients with previously treated stage IB-IVA mycosis fungoides/Seezary syndrome. Br. J. Dermatol. 175, 80–88.
Chiyomaru, T., Yamamura, S., Fukuhara, S., Hidaka, H., Majid, S., Saini, S., Arora, S., Deng, G.R., Shahryari, V., Chang, I., Tanaka, Y., Tabatabai, Z.L., Enokida, H., Seki, N., Nakagawa, M., Dahiya, R., 2013. Genistein up-regulates tumor suppressor MicroRNA-574-3p in prostate cancer. PloS One 8.
Choi, S.Y., Kee, H.J., Jin, L., Ryu, Y., Sun, S., Kim, G.R., Jeong, M.H., 2018. Inhibition of class IIa histone deacetylase activity by gallic acid, sulforaphane, TMP269, and panobinostat. Biomed. Pharmacother. 101, 145–154.
Christman, J.K., 2002. 5-Azacytidine and 5-aza-2 '-deoxycytidine as inhibitors of DNA methylation: mechanistic studies and their implications for cancer therapy. Oncogene 21, 5483–5495.
Connolly, R.M., Li, H., Jankowitz, R.C., Zhang, Z., Rudek, M.A., Jeter, S.C., Slater, S.A., Powers, P., Wolff, A.C., Fetting, J.H., Brufsky, A., Piekarz, R., Ahuja, N., Laird, P.W., Shen, H., Weisenberger, D.J., Cope, L., Herman, J.G., Somlo, G., Garcia, A.A., Jones, P.A., Baylin, S.B., Davidson, N.E., Zahnow, C.A., Stearns, V., 2017. Combination epigenetic therapy in advanced breast cancer with 5-azacitidine and entinostat: a phase II national cancer institute/stand up to cancer study. Clin. Canc. Res. 23, 2691–2701.
Coyne, G.O.S., Chen, A.P., Kummar, S., Meehan, R.S., Collins, J., Zlott, J., Kelly, K., Lenz, H.J., Newman, E.M., Morgan, R., Juwara, L., Eiseman, J., Beumer, J.H., Tomaszewski, J., Doroshow, J., 2016. Phase I trial of oral 5-fluoro-2 '-deoxycytidine with oral tetrahydrouridine in patients with advanced solid tumors. Eur. J. Canc. 69 S90-S90.
Dagdemir, A., Durif, J., Ngollo, M., Bignon, Y.J., Bernard-Gallon, D., 2013. Histone lysine trimethylation or acetylation can be modulated by phytoestrogen, estrogen or anti-HDAC in breast cancer cell lines. Epigenomics-Uk 5, 51–63.
Daige, C., Priddy, L., Wiggins, J., Nelligan-Davis, T., Enzler, D., Vadnagara, K., Brown, D., 2016. MRX34, a liposomal miR-34 mimic and potential firstin-class microRNA therapeutic: activity in animal models of liver cancer. J. Clin. Oncol. 34.
Datta, J., Ghoshal, K., Denny, W.A., Gamage, S.A., Brooke, D.G., Phiasivongsa, P., Redkar, S., Jacob, S.T., 2009. A new class of quinoline-based DNA hypomethylating agents reactivates tumor suppressor genes by blocking DNA methyltransferase 1 activity and inducing its degradation. Cancer Res. 69, 4277–4285.
de Bono, J.S., Kristeleit, R., Tolcher, A., Fong, P., Pacey, S., Karavasilis, V., Mita, M., Shaw, H., Workman, P., Kaye, S., Rowinsky, E.K., Aherne, W., Atadja, P., Scott, J.W., Patnaik, A., 2008. Phase I pharmacokineitic and pharmacodynamic study of LAQ824, a hydroxamate histone deacetylase inhibitor with a heat shock protein-90 inhibitory profile, in patients with advanced solid tumors. Clin. Canc. Res. 14, 6663–6673.
de Conti, A., Tryndyak, V., Koturbash, I., Heidor, R., Kuroiwa-Trzmielina, J., Ong, T.P., Beland, F.A., Moreno, F.S., Pogribny, I.P., 2013. The chemopreventive activity of the butyric acid prodrug tributyrin in experimental rat hepatocarcinogenesis is associated with p53 acetylation and activation of the p53 apoptotic signaling pathway. Carcinogenesis 34, 1900–1906.
de la Parra, C., Castillo-Pichardo, L., Cruz-Collazo, A., Cubano, L., Redis, R., Calin, G.A., Dharmawardhane, S., 2016. Soy isoflavone genistein-mediated downregulation of miR-155 contributes to the anticancer effects of genistein. Nutr. Canc. 68, 154–164.
Deb, G., Thakur, V.S., Limaye, A.M., Gupta, S., 2015. Epigenetic induction of tissue inhibitor of matrix metalloproteinase-3 by green tea polyphenols in breast cancer cells. Mol. Carcinog. 54, 485–499.
Deng, L., Yang, S.B., Xu, F.F., Zhang, J.H., 2015. Long noncoding RNA CCAT1 promotes hepatocellular carcinoma progression by functioning as let-7 sponge. J. Exp. Clin. Canc. Res. 34.
Deubzer, H.E., Ehemann, V., Westermann, F., Heinrich, R., Mechtersheimer, G., Kulozik, A.E., Schwab, M., Witt, O., 2008. Histone deacetylase inhibitor Helminthosporium carbonum (HC)-toxin suppresses the malignant phenotype of neuroblastoma cells. Int. J. Canc. 122, 1891–1900.
Deutsch, E., Moyal, E.C.-J., Gregorc, V., Zucali, P.A., Menard, J., Soria, J.-C., Kloos, I., Hsu, J., Luan, Y., Liu, E., Vezan, R., Graef, T., Rivera, S., 2017. A phase 1 dose-escalation study of the oral histone deacetylase inhibitor abexinostat in combination with standard hypofractionated radiotherapy in advanced solid tumors. Oncotarget 8, 56199–56209.
Devarshi, P.P., Jones, A.D., Taylor, E.M., Stefanska, B., Henagan, T.M., 2017. Quercetin and quercetin-rich red onion extract alter pgc-1 alpha promoter methylation and splice variant expression. PPAR Res. 8.
Devi, K.P., Rajavel, T., Daglia, M., Nabavi, S.F., Bishayee, A., Nabavi, S.M., 2017. Targeting miRNAs by polyphenols: novel therapeutic strategy for cancer. Semin. Canc. Biol. 46, 146–157.
Dhar, S., Kumar, A., Rimando, A.M., Zhang, X., Levenson, A.S., 2015. Resveratrol and pterostilbene epigenetically restore PTEN expression by targeting oncomiRs of the miR-17 family in prostate cancer. Oncotarget 6, 27214–27226.
Dou, H.Q., Shen, R.H., Tao, J.X., Huang, L.C., Shi, H.Z., Chen, H., Wang, Y.X., Wang, T., 2017. Curcumin suppresses the colon cancer proliferation by inhibiting Wnt/beta-catenin pathways via miR-130a. Front. Pharmacol. 8.
Druesne, N., Pagniez, A., Mayeur, C., Thomas, M., Cherbuy, C., Duee, P.H., Martel, P., Chaumontet, C., 2004. Diallyl disulfide (DADS) increases histone acetylation and p21(waf1/cip1) expression in human colon tumor cell lines. Carcinogenesis 25, 1227–1236.
Du, L.P., Xie, Z.L., Wu, L.C., Chiu, M., Lin, J.Y., Chan, K.K., Liu, S.J., Liu, Z.F., 2012. Reactivation of RASSF1A in breast cancer cells by curcumin. Nutr. Canc. 64, 1228–1235.
Duvic, M., Bates, S.E., Piekarz, R., Eisch, R., Kim, Y.H., Lerner, A., Robak, T., Samtsov, A., Becker, J.C., McCulloch, W., Waksman, J., Whittaker, S., 2018. Responses to romidepsin in patients with cutaneous T-cell lymphoma and prior treatment with systemic chemotherapy. Leuk. Lymphoma 59, 880–887.
Egger, G., Liang, G.N., Aparicio, A., Jones, P.A., 2004. Epigenetics in human disease and prospects for epigenetic therapy. Nature 429, 457–463.
Eigl, B.J., North, S., Winquist, E., Finch, D., Wood, L., Sridhar, S.S., Powers, J., Good, J., Sharma, M., Squire, J.A., Bazov, J., Jamaspishvili, T., Cox, M.E., Bradbury, P.A., Eisenhauer, E.A., Chi, K.N., 2015. A phase II study of the HDAC inhibitor SB939 in patients with castration resistant prostate cancer: NCIC clinical trials group study IND195. Invest. N. Drugs 33, 969–976.
Faghihloo, E., Araei, Y., Mohammadi, M., Mirzaei, H., Mohammadi, H.R., Mokhtari-Azad, T., 2016. The effect of oxamflatin on the E-cadherin expression in gastric cancer cell line. Cancer Gene Ther. 23, 396–399.
Fedyanin, M., Tjulandin, S., Cheporov, S., Vladimirov, V., Moiseenko, V., Orlov, S., Manikhas, G., Cakana, A., Azarova, V., Karavaeva, O., Vostokova, N., Baranovskiy, S., 2016. Phase I dose of oral quisinostat, in combination with gemcitabine (G) and cisplatin (Cis) or paclitaxel (P) and carboplatin (Carbo) in patients (pts) with non-small cell lung cancer or ovarian cancer (OC). Ann. Oncol. 27.
Fenech, M., 2012. Folate (vitamin B9) and vitamin B12 and their function in the maintenance of nuclear and mitochondrial genome integrity. Mutat. Res. Fund Mol. Mech. Mutagen 733, 21–33.
Fernandes, G.F.S., Silva, G.D.B., Pavan, A.R., Chiba, D.E., Chin, C.M., Dos Santos, J.L., 2017. Epigenetic regulatory mechanisms induced by resveratrol. Nutrients 9, 27.
Foulks, J.M., Parnell, K.M., Nix, R.N., Chau, S., Swierczek, K., Saunders, M., Wright, K., Hendrickson, T.F., Ho, K.-K., McCullar, M.V., Kanner, S.B., 2012. Epigenetic drug discovery: targeting DNA methyltransferases. J. Biomol. Screen 17, 2–17.
Fu, M., Wan, F., Li, Z., Zhang, F., 2016. 4SC-202 activates ASK1-dependent mitochondrial apoptosis pathway to inhibit hepatocellular carcinoma cells. Biochem Bioph Res Co 471, 267–273.
Furumai, R., Matsuyama, A., Kobashi, N., Lee, K.H., Nishiyama, N., Nakajima, I., Tanaka, A., Komatsu, Y., Nishino, N., Yoshida, M., Horinouchi, S., 2002. FK228 (depsipeptide) as a natural prodrug that inhibits class I histone deacetylases. Cancer Res. 62, 4916–4921.
Gallant-Behm, C.L., Maari, C., Jackson, A.L., Seto, A.G., Lynch, J.M., Ruckman, J., Landry, M.L., Pestano, L.A., Dickinson, B.A., Dalby, C.M., Sanseverino, M., Rodman, D.M., Gordon, G.G., Rubin, P., Marshall, W.S., 2017. Pharmacodynamic activity of a microRNA-29b mimic (MRG-201) in human skin incisions. J. Invest. Dermatol. 137 B4-B4.
Galli, M., Salmoiraghi, S., Golay, J., Gozzini, A., Crippa, C., Pescosta, N., Rambaldi, A., 2010. A phase II multiple dose clinical trial of histone deacetylase inhibitor ITF2357 in patients with relapsed or progressive multiple myeloma. Ann. Hematol. 89, 185–190.
Gambari, R., Brognara, E., Spandidos, D.A., Fabbri, E., 2016. Targeting oncomiRNAs and mimicking tumor suppressor miRNAs: new trends in the development of miRNA therapeutic strategies in oncology. Int. J. Oncol. 49, 5–32.

Gao, A.M., Zhang, X.Y., Hu, J.N., Ke, Z.P., 2018a. Apigenin sensitizes hepatocellular carcinoma cells to doxorubic through regulating miR-520b/ATG7 axis. Chem. Biol. Interact. 280, 45–50.
Gao, A.M., Zhang, X.Y., Ke, Z.P., 2017. Apigenin sensitizes BEL-7402/ADM cells to doxorubicin through inhibiting miR-101/Nrf2 pathway. Oncotarget 8, 82085–82091.
Gao, L., Cheng, D., Yang, J., Wu, R., Li, W., Kong, A.-N., 2018b. Sulforaphane epigenetically demethylates the CpG sites of the miR-9-3 promoter and reactivates miR-9-3 expression in human lung cancer A549 cells. J. Nutr. Biochem. 56, 109–115.
Garzon, R., Liu, S., Fabbri, M., Liu, Z., Heaphy, C.E.A., Callegari, E., Schwind, S., Pang, J., Yu, J., Muthusamy, N., Havelange, V., Volinia, S., Blum, W., Rush, L.J., Perrotti, D., Andreeff, M., Bloomfield, C.D., Byrd, J.C., Chan, K., Wu, L.-C., Croce, C.M., Marcucci, G., 2009. MicroRNA-29b induces global DNA hypomethylation and tumor suppressor gene reexpression in acute myeloid leukemia by targeting directly DNMT3A and 3B and indirectly DNMT1. Blood 113, 6411–6418.
Gediya, L.K., Belosay, A., Khandelwal, A., Purushottamachar, P., Njar, V.C.O., 2008. Improved synthesis of histone deacetylase inhibitors (HDIs) (MS-275 and CI-994) and inhibitory effects of HDIs alone or in combination with RAMBAs or retinoids on growth of human LNCaP prostate cancer cells and tumor xenografts. Bioorg. Med. Chem. 16, 3352–3360.
Graca, I., Sousa, E.J., Baptista, T., Almeida, M., Ramalho-Carvalho, J., Palmeira, C., Henrique, R., Jeronimo, C., 2014a. Anti-tumoral effect of the non-nucleoside DNMT inhibitor RG108 in human prostate cancer cells. Curr. Pharmaceut. Des. 20, 1803–1811.
Graca, I., Sousa, E.J., Costa-Pinheiro, P., Vieira, F.Q., Torres-Ferreira, J., Martins, M.G., Henrique, R., Jeronimo, C., 2014b. Anti-neoplastic properties of hydralazine in prostate cancer. Oncotarget 5, 5950–5964.
Greve, G., Schiffmann, I., Pfeifer, D., Pantic, M., Schuler, J., Lubbert, M., 2015. The pan-HDAC inhibitor panobinostat acts as a sensitizer for erlotinib activity in EGFR-mutated and -wildtype non-small cell lung cancer cells. BMC Canc. 15, 10.
Guo, L., Xu, K., Yan, H.B., Feng, H.F., Wang, T., Chai, L.L., Xu, G.Z., 2017. MicroRNA expression signature and the therapeutic effect of the microRNA-21 antagomir in hypertrophic scarring. Mol. Med. Rep. 15, 1211–1221.
Guo, Y., Shu, L.M., Zhang, C.Y., Su, Z.Y., Kong, A.N.T., 2015. Curcumin inhibits anchorage-independent growth of HT29 human colon cancer cells by targeting epigenetic restoration of the tumor suppressor gene DLEC1. Biochem. Pharmacol. 94, 69–78.
Ha, M.K., Song, Y.H., Jeong, S.J., Lee, H.J., Jung, J.H., Kim, B., Song, H.S., Huh, J.E., Kim, S.H., 2011. Emodin inhibits proinflammatory responses and inactivates histone deacetylase 1 in hypoxic rheumatoid synoviocytes. Biol. Pharm. Bull. 34, 1432–1437.
Haberland, M., Montgomery, R.L., Olson, E.N., 2009. The many roles of histone deacetylases in development and physiology: implications for disease and therapy. Nat. Rev. Genet. 10, 32–42.
Hanke, N.T., Garland, L.L., Baker, A.F., 2016. Carfilzomib combined with suberanilohydroxamic acid (SAHA) synergistically promotes endoplasmic reticulum stress in non-small cell lung cancer cell lines. J Cancer Res Clin 142, 549–560.
Hansen, T.B., Jensen, T.I., Clausen, B.H., Bramsen, J.B., Finsen, B., Damgaard, C.K., Kjems, J., 2013. Natural RNA circles function as efficient microRNA sponges. Nature 495, 384–388.
Hassanzadeh, M., Kasymov, R., Mahernia, S., Adib, M., Emperle, M., Dukatz, M., Bashtrykov, P., Jeltsch, A., Amanlou, M., 2017. Discovery of novel and selective DNA methyltransferase 1 inhibitors by pharmacophore and docking-based virtual screening. Chemistry 2, 8383–8392.
He, W.-L., Li, Y.-H., Hou, W.-J., Ke, Z.-F., Chen, X.-L., Lu, L.-Y., Cai, S.-R., Song, W., Zhang, C.-H., He, Y.-L., 2014. RAD51 potentiates synergistic effects of chemotherapy with PCI-24781 and cis-diamminedichloroplatinum on gastric cancer. World J. Gastroenterol. 20, 10094–10107.
Hodjat, M., Rahmani, S., Khan, F., Niaz, K., Navaei-Nigjeh, M., Nejad, S.M., Abdollahi, M., 2017. Environmental toxicants, incidence of degenerative diseases, and therapies from the epigenetic point of view. Arch. Toxicol. 91, 2577–2597.
Hsu, A., Wong, C.P., Yu, Z., Williams, D.E., Dashwood, R.H., Ho, E., 2011. Promoter demethylation of cyclin D2 by sulforaphane in prostate cancer cells. Clin. Epigenet. 3.
Huang, S.S., Ding, D.F., Chen, S., Dong, C.L., Ye, X.L., Yuan, Y.G., Feng, Y.M., You, N., Xu, J.R., Miao, H., You, Q., Lu, X., Lu, Y.B., 2017. Resveratrol protects podocytes against apoptosis via stimulation of autophagy in a mouse model of diabetic nephropathy. Sci Rep-Uk 7, 15.
Huang, Z., Wang, S., Min, H., Li, J., Qin, L.-s., Li, D., 2016. Pre-clinical characterization of 4SC-202, a novel class I HDAC inhibitor, against colorectal cancer cells. Tumor Biol. 37, 10257–10267.
Hummel-Eisenbeiss, J., Hascher, A., Hals, P.-A., Sandvold, M.L., Mueller-Tidow, C., Lyko, F., Rius, M., 2013. The role of human equilibrative nucleoside transporter 1 on the cellular transport of the DNA methyltransferase inhibitors 5-azacytidine and CP-4200 in human leukemia cells. Mol. Pharmacol. 84, 438–450.
Izbicka, E., Macdonald, J.R., Davidson, K., Lawrence, R.A., Gomez, L., Von Hoff, D.D., 1999. 5,6 dihydro-5 '-azacytidine (DHAC) restores androgen responsiveness in androgen-insensitive prostate cancer cells. Anticancer Res. 19, 1285–1291.
Izzotti, A., Larghero, P., Cartiglia, C., Longobardi, M., Pfeffer, U., Steele, V.E., De Flora, S., 2010. Modulation of microRNA expression by budesonide, phenethyl isothiocyanate and cigarette smoke in mouse liver and lung. Carcinogenesis 31, 894–901.
Janssens, G.O., Rademakers, S.E., Terhaard, C.H., Doornaert, P.A., Bijl, H.P., van den Ende, P., Chin, A., Marres, H.A., de Bree, R., van der Kogel, A.J., Hoogsteen, I.J., Bussink, J., Span, P.N., Kaanders, J.H., 2012. Accelerated radiotherapy with carbogen and nicotinamide for laryngeal cancer: results of a phase III randomized trial. J. Clin. Oncol. 30, 1777–1783.
Jeong, J.B., Choi, J., Lou, Z.Y., Jiang, X.J., Lee, S.H., 2013. Patchouli alcohol, an essential oil of Pogostemon cablin, exhibits anti-tumorigenic activity in human colorectal cancer cells. Int. Immunopharm. 16, 184–190.
Jia, J., Chen, J., 2008. Histone hyperacetylation is involved in the quercetin-induced human leukemia cell death. Pharmazie 63, 379–383.
Jiang, L.L., Zhou, S.J., Zhang, X.M., Chen, H.Q., Liu, W., 2016. Sulforaphane suppresses in vitro and in vivo lung tumorigenesis through downregulation of HDAC activity. Biomed. Pharmacother. 78, 74–80.
Johnson, I.T., 2018. Cruciferous vegetables and risk of cancers of the gastrointestinal tract. Mol. Nutr. Food Res. 62 (S1), e1701000.
Johnson, M.L., Adjei, A.A., Ramalingam, S.S., Janne, P.A., Dominguez, G., Gabrilovich, D., Deleon, L., Hasapidis, J.L., Diede, S.J., Ordentlich, P., Hellmann, M.D., 2016. Preliminary results of ENCORE 601, a phase 1 b/2, open-label study of entinostat (ENT) in combination with pembrolizumab (PEMBRO) in patients with non-small cell lung cancer (NSCLC). J. Clin. Oncol. 34.
Joung, K.E., Kim, D.K., Sheen, Y.Y., 2004. Antiproliferative effect of trichostatin A and HC-toxin in T47D human breast cancer cells. Arch Pharm. Res. (Seoul) 27, 640–645.
Jueliger, S., Lyons, J., Cannito, S., Pata, I., Pata, P., Shkolnaya, M., Lo Re, O., Peyrou, M., Villarroya, F., Pazienza, V., Rappa, F., Cappello, F., Azab, M., Taverna, P., Vinciguerra, M., 2016. Efficacy and epigenetic interactions of novel DNA hypomethylating agent guadecitabine (SGI-110) in preclinical models of hepatocellular carcinoma. Epigenetics 1–12.
Kala, R., Shah, H.N., Martin, S.L., Tollefsbol, T.O., 2015. Epigenetic-based combinatorial resveratrol and pterostilbene alters DNA damage response by affecting SIRT1 and DNMT enzyme expression, including SIRT1-dependent gamma-H2AX and telomerase regulation in triple-negative breast cancer. BMC Canc. 15.
Kala, R., Tollefsbol, T.O., 2016. A novel combinatorial epigenetic therapy using resveratrol and pterostilbene for restoring estrogen receptor-alpha (ER alpha) expression in ER alpha-negative breast cancer cells. PloS One 11.
Kam, A., Li, K.M., Razmovski-Naumovski, V., Nammi, S., Chan, K., Li, G.Q., 2014. Gallic acid protects against endothelial injury by restoring the depletion of DNA methyltransferase 1 and inhibiting proteasome activities. Int. J. Cardiol. 171, 231–242.
Kaminskas, E., Farrell, A.T., Wang, Y.C., Sridhara, R., Pazdur, R., 2005. FDA drug approval summary: azacitidine (5-azacytidine, Vidaza((TM))) for injectable suspension. Oncol 10, 176–182.
Kantarjian, H.M., Roboz, G.J., Kropf, P.L., Yee, K.W.L., O'Connell, C.L., Tibes, R., Walsh, K.J., Podoltsev, N.A., Griffiths, E.A., Jabbour, E., Garcia-Manero, G., Rizzieri, D., Stock, W., Savona, M.R., Rosenblat, T.L., Berdeja, J.G., Ravandi, F., Rock, E.P., Hao, Y., Azab, M., Issa, J.-P.J., 2017. Guadecitabine (SGI-110) in treatment-naive patients with acute myeloid leukaemia: phase 2 results from a multicentre, randomised, phase 1/2 trial. Lancet Oncol. 18, 1317–1326.
Keen, J.C., Yan, L., Mack, K.M., Pettit, C., Smith, D., Sharma, D., Davidson, N.E., 2003. A novel histone deacetylase inhibitor, Scriptaid, enhances expression of functional estrogen receptor alpha (ER) in ER negative human breast cancer cells in combination with 5-aza 2 '-deoxycytidine. Breast Canc. Res. Treat. 81, 177–186.
Kelnar, K., Peltier, H.J., Bader, A.G., 2016. Down-regulation of target gene expression in human white blood cells (hWBCs) by MRX34, a liposomal miR-34 mimic: next generation sequencing (NGS) results from a first-in-human trial of microRNA cancer therapy. Ann. Oncol. 27.
Khan, M.A., Hussain, A., Sundaram, M.K., Alalami, U., Gunasekera, D., Ramesh, L., Hamza, A., Quraishi, U., 2015. (-)-Epigallocatechin-3-gallate reverses the expression of various tumor-suppressor genes by inhibiting DNA methyltransferases and histone deacetylases in human cervical cancer cells. Oncol. Rep. 33, 1976–1984.
Kikuno, N., Shiina, H., Urakami, S., Kawamoto, K., Hirata, H., Tanaka, Y., Majid, S., Igawa, M., Dahiya, R., 2017. Genistein mediated histone acetylation and demethylation activates tumor suppressor genes in prostat cancer cells' (Retraction of Vol 123, Pg 552, 2008). Int. J. Canc. 141 1492-1492.
Kim, H., Banerjee, N., Barnes, R.C., Pfent, C.M., Talcott, S.T., Dashwood, R.H., Mertens-Talcott, S.U., 2017. Mango polyphenolics reduce inflammation in intestinal colitis-sinvolvement of the miR-126/PI3K/AKT/mTOR axis in vitro and in vivo. Mol. Carcinog. 56, 197–207.
Kirschbaum, M.H., Foon, K.A., Frankel, P., Ruel, C., Pulone, B., Tuscano, J.M., Newman, E.M., 2014. A phase 2 study of belinostat (PXD101) in patients with relapsed or refractory acute myeloid leukemia or patients over the age of 60 with newly diagnosed acute myeloid leukemia: a California Cancer Consortium Study. Leuk. Lymphoma 55, 2301–2304.
Klisovic, R.B., Stock, W., Cataland, S., Klisovic, M.I., Liu, S., Bium, W., Green, M., Odenike, O., Godley, L., Burgt, J.V., Van Laar, E., Cullen, M., Macleod, A.R., Besterman, J.M., Reid, G.K., Byrd, J.C., Marcuccil, G., 2008. A phase I biological study of MG98, an oligodeoxynucleotide antisense to DNA methyltransferase 1, in patients with high-risk myelodysplasia and acute myeloid leukemia. Clin. Canc. Res. 14, 2444–2449.
Kulcheski, F.R., Christoff, A.P., Margis, R., 2016. Circular RNAs are miRNA sponges and can be used as a new class of biomarker. J. Biotechnol. 238, 42–51.
Kumar, L., Shamsuzzama, Haque, R., Baghel, T., Nazir, A., 2017a. Circular RNAs: the emerging class of non-coding RNAs and their potential role in human neurodegenerative diseases. Mol. Neurobiol. 54, 7224–7234.
Kumar, U., Sharma, U., Rathi, G., 2017b. Reversal of hypermethylation and reactivation of glutathione S-transferase pi 1 gene by curcumin in breast cancer cell line. Tumor Biol. 39.
Laubach, J.P., Moreau, P., San-Miguel, J.F., Richardson, P.G., 2015. Panobinostat for the treatment of multiple myeloma. Clin. Canc. Res. 21, 4767–4773.
Lee, H.Y., Lee, H.Y., Choi, J.Y., Hur, J., Kim, I.K., Kim, Y.K., Kang, J.Y., Lee, S.Y., 2017. Inhibition of MicroRNA-21 by an antagomir ameliorates allergic inflammation in a mouse model of asthma. Exp. Lung Res. 43, 109–119.
Lee, M., Son, M., Ryu, E., Shin, Y.S., Kim, J.G., Kang, B.W., Sung, G.H., Cho, H., Kang, H., 2015. Quercetin-induced apoptosis prevents EBV infection. Oncotarget 6, 12603–12624.
Lee, P.S., Chiou, Y.S., Ho, C.T., Pan, M.H., 2018. Chemoprevention by resveratrol and pterostilbene: targeting on epigenetic regulation. Biofactors 44, 26–35.

Lee, W.J., Chen, Y.R., Tseng, T.H., 2011. Quercetin induces FasL-related apoptosis, in part, through promotion of histone H3 acetylation in human leukemia HL-60 cells. Oncol. Rep. 25, 583–591.
Lewinska, A., Adamczyk-Grochala, J., Deregowska, A., Wnuk, M., 2017. Sulforaphane-induced cell cycle arrest and senescence are accompanied by DNA hypomethylation and changes in microRNA profile in breast cancer cells. Theranostics 7, 3461–3477.
Li, B., Shi, C., Li, B., Zhao, J.M., Wang, L., 2018a. The effects of Curcumin on HCT-116 cells proliferation and apoptosis via the miR-491/PEG10 pathway. J. Cell. Biochem. 119, 3091–3098.
Li, F., Zhang, L.Y., Li, W., Deng, J.Q., Zheng, J., An, M.X., Lu, J.C., Zhou, Y.F., 2015a. Circular RNA ITCH has inhibitory effect on ESCC by suppressing the Wnt/beta-catenin pathway. Oncotarget 6, 6001–6013.
Li, H., Xu, W.J., Huang, Y.M., Huang, X., Xu, L.C., Lv, Z.B., 2012. Genistein demethylates the promoter of CHD5 and inhibits neuroblastoma growth in vivo. Int. J. Mol. Med. 30, 1081–1086.
Li, H.J., Li, X., Pang, H., Pan, J.J., Xie, X.J., Chen, W., 2015b. Long non-coding RNA UCA1 promotes glutamine metabolism by targeting miR-16 in human bladder cancer. Jpn. J. Clin. Oncol. 45, 1055–1063.
Li, S.B., Guo, J.Y., Ying, Z.F., Chen, S., Yang, L., Chen, K.S., Long, Q., Qin, D.J., Pei, D.Q., Liu, X.G., 2015c. Valproic acid-induced hepatotoxicity in alpers syndrome is associated with mitochondrial permeability transition pore opening-dependent apoptotic sensitivity in an induced pluripotent stem cell model. Hepatology 61, 1730–1739.
Li, W., Liu, M., Xu, Y.F., Feng, Y., Che, J.P., Wang, G.C., Zheng, J.H., 2014. Combination of quercetin and hyperoside has anticancer effects on renal cancer cells through inhibition of oncogenic microRNA-27a. Oncol. Rep. 31, 117–124.
Li, W.D., Yang, W.N., Liu, Y.J., Chen, S.Y., Chin, S.M., Qi, X.L., Zhao, Y.C., Liu, H., Wang, J.S., Mei, X.T., Huang, P.G., Xu, D.H., 2017. MicroRNA-378 enhances inhibitory effect of curcumin on glioblastoma. Oncotarget 8, 73938–73946.
Li, W.J., Su, Z.Y., Guo, Y., Zhang, C.Y., Wu, R.Y., Gao, L.B., Zheng, X., Du, Z.Y., Zhang, K., Kong, A.N., 2018b. Curcumin derivative epigenetically reactivates Nrf2 antioxidative stress signaling in mouse prostate cancer TRAMP C1 cells. Chem. Res. Toxicol. 31, 88–96.
Li, Y.-C., Wang, Y., Li, D.-D., Zhang, Y., Zhao, T.-C., Li, C.-F., 2018c. Procaine is a specific DNA methylation inhibitor with anti-tumor effect for human gastric cancer. J. Cell. Biochem. 119, 2440–2449.
Li, Y.Y., Meeran, S.M., Patel, S.N., Chen, H.P., Hardy, T.M., Tollefsbol, T.O., 2013. Epigenetic reactivation of estrogen receptor-alpha (ER alpha) by genistein enhances hormonal therapy sensitivity in ER alpha-negative breast cancer. Mol. Canc. 12.
Li, Z., Liu, Y.H., Diao, H.Y., Ma, J., Yao, Y.L., 2016. Long noncoding RNA NEAT1 promotes glioma pathogenesis by regulating miR-449b-5p/c-Met axis. Tumor Biol. 37, 673–683.
Liang, S., Nie, Z.-W., Guo, J., Niu, Y.-J., Shin, K.-T., Ock, S.A., Cui, X.-S., 2018. Overexpression of MicroRNA-29b decreases expression of DNA methyltransferases and improves quality of the blastocysts derived from somatic cell nuclear transfer in cattle. Microsc. Microanal. 24, 29–37.
Liang, W.C., Fu, W.M., Wong, C.W., Wang, Y., Wang, W.M., Hu, G.X., Zhang, L., Xiao, L.J., Wan, D.C.C., Zhang, J.F., Waye, M.M.Y., 2015. The lncRNA H19 promotes epithelial to mesenchymal transition by functioning as miRNA sponges in colorectal cancer. Oncotarget 6, 22513–22525.
Liang, W.N., Li, X.H., Li, Y.C., Li, C.D., Gao, B.Z., Gan, H.J., Li, S.M., Shen, J.Y., Kang, J., Ding, S.S., Lin, X.J., Liao, L.H., 2014. Gallic acid induces apoptosis and inhibits cell migration by upregulating miR-518b in SW1353 human chondrosarcoma cells. Int. J. Oncol. 44, 91–98.
Lin, J.Q., Gilbert, J., Rudek, M.A., Zwiebel, J.A., Gore, S., Jiemjit, A., Zhao, M., Baker, S.D., Ambinder, R.F., Herman, J.G., Donehower, R.C., Carducci, M.A., 2009. A phase I dose-finding study of 5-azacytidine in combination with sodium phenylbutyrate in patients with refractory solid tumors. Clin. Canc. Res. 15, 6241–6249.
Lin, R.K., Hsu, C.H., Wang, Y.C., 2007. Mithramycin A inhibits DNA methyltransferase and metastasis potential of lung cancer cells. Anti Canccer Drugs 18, 1157–1164.
Liu, D., Perkins, J.T., Hennig, B., 2016a. EGCG prevents PCB-126-induced endothelial cell inflammation via epigenetic modifications of NF-kappa B target genes in human endothelial cells. J. Nutr. Biochem. 28, 164–170.
Liu, H., Li, W., Zhao, S.J., Zhang, X.M., Zhang, M.L., Xiao, Y.Y., Wilson, J.X., Huang, G.W., 2016b. Folic acid attenuates the effects of amyloid beta oligomers on DNA methylation in neuronal cells. Eur. J. Nutr. 55, 1849–1862.
Liu, J.B., Li, M., Wang, Y.W., Luo, J.C., 2017a. Curcumin sensitizes prostate cancer cells to radiation partly via epigenetic activation of miR-143 and miR-143 mediated autophagy inhibition. J. Drug Target. 25, 645–652.
Liu, T., Zu, C.H., Wang, S.S., Song, H.L., Wang, Z.L., Xu, X.N., Liu, H.S., Wang, Y.L., Shen, Z.Y., 2016c. PIK3C2A mRNA functions as a miR-124 sponge to facilitate CD151 expression and enhance malignancy of hepatocellular carcinoma cells. Oncotarget 7, 43376–43389.
Liu, W.L., Chang, J.M., Chong, I.W., Hung, Y.L., Chen, Y.H., Huang, W.T., Kuo, H.F., Hsieh, C.C., Liu, P.L., 2017b. Curcumin inhibits LIN-28a through the activation of miRNA-98 in the lung cancer cell line A549. Molecules 22.
Liu, Z.H., Li, J., Xia, J., Jiang, R., Zuo, G.W., Li, X.P., Chen, Y., Xiong, W., Chen, D.L., 2015. Ginsenoside 20(s)-Rh2 as potent natural histone deacetylase inhibitors suppressing the growth of human leukemia cells. Chem. Biol. Interact. 242, 227–234.
Lu, J., Getz, G., Miska, E.A., Alvarez-Saavedra, E., Lamb, J., Peck, D., Sweet-Cordero, A., Ebet, B.L., Mak, R.H., Ferrando, A.A., Downing, J.R., Jacks, T., Horvitz, H.R., Golub, T.R., 2005. MicroRNA expression profiles classify human cancers. Nature 435, 834–838.
Lubecka-Pietruszewska, K., Kaufman-Szymczyk, A., Stefanska, B., Cebula-Obrzut, B., Smolewski, P., Fabianowska-Majewska, K., 2015. Sulforaphane alone and in combination with clofarabine epigenetically regulates the expression of DNA methylation-silenced tumour suppressor genes in human breast cancer cells. J. Nutrigenetics Nutrigenomics 8, 91–101.
Luger, S.M., O'Connell, C.L., Klimek, V., Cooper, M.A., Besa, E.C., Rossetti, J.M., Reid, G.K., Humphrey, R., Martell, R.E., Garcia-Manero, G., 2013. A phase II study of mocetinostat, an oral isotype-selective histone deacetylase (HDAC) inhibitor, in combination with 5-azacitidine in patients with myelodysplastic syndrome (MDS). J. Clin. Oncol. 31.
Ma, L., Reinhardt, F., Pan, E., Soutschek, J., Bhat, B., Marcusson, E.G., Teruya-Feldstein, J., Bell, G.W., Weinberg, R.A., 2010. Therapeutic silencing of miR-10b inhibits metastasis in a mouse mammary tumor model. Nat. Biotechnol. 28, 341–U367.
Ma, Y.N., Chen, M.T., Wu, Z.K., Zhao, H.L., Yu, H.C., Yu, J., Zhang, J.W., 2013. Emodin can induce K562 cells to erythroid differentiation and improve the expression of globin genes. Mol. Cell. Biochem. 382, 127–136.
Madunic, J., Madunic, I.V., Gajski, G., Popic, J., Garaj-Vrhovac, V., 2018. Apigenin: a dietary flavonoid with diverse anticancer properties. Cancer Lett. 413, 11–22.
Mahajan, S.S., Scian, M., Sripathy, S., Posakony, J., Lao, U., Loe, T.K., Leko, V., Thalhofer, A., Schuler, A.D., Bedalov, A., Simon, J.A., 2014. Development of pyrazolone and isoxazol-5-one cambinol analogues as sirtuin inhibitors. J. Med. Chem. 57, 3283–3294.
Mann, B.S., Johnson, J.R., Cohen, M.H., Justice, R., Pazdur, R., 2007. FDA approval summary: vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. Oncol 12, 1247–1252.
Martin, S.L., Kala, R., Tollefsbol, T.O., 2018. Mechanisms for the inhibition of colon cancer cells by sulforaphane through epigenetic modulation of MicroRNA-21 and human telomerase reverse transcriptase (hTERT) down-regulation. Curr. Cancer Drug Targets 18, 97–106.
Mawatari, T., Ninomiya, I., Inokuchi, M., Harada, S., Hayashi, H., Oyama, K., Makino, I., Nakagawara, H., Miyashita, T., Tajima, H., Takamura, H., Fushida, S., Ohta, T., 2015. Valproic acid inhibits proliferation of HER2-expressing breast cancer cells by inducing cell cycle arrest and apoptosis through Hsp70 acetylation. Int. J. Oncol. 47, 2073–2081.
McGee, M., Bainbridge, S., Fontaine-Bisson, B., 2018. A crucial role for maternal dietary methyl donor intake in epigenetic programming and fetal growth outcomes. Nutr. Rev. 76, 469–478.
Mendez-Lucio, O., Tran, J., Medina-Franco, J.L., Meurice, N., Muller, M., 2014. Toward drug repurposing in epigenetics: olsalazine as a hypomethylating compound active in a cellular context. ChemMedChem 9, 560–565.
Mirza, S., Sharma, G., Parshad, R., Gupta, S.D., Pandya, P., Ralhan, R., 2013. Expression of DNA methyltransferases in breast cancer patients and to analyze the effect of natural compounds on DNA methyltransferases and associated proteins. J Breast Cancer 16, 23–31.
Mirzaei, H., Masoudifar, A., Sahebkar, A., Zare, N., Nahand, J.S., Rashidi, B., Mehrabian, E., Mohammadi, M., Mirzaei, H.R., Jaafari, M.R., 2018. MicroRNA: a novel target of curcumin in cancer therapy. J. Cell. Physiol. 233, 3004–3015.
Montalban-Bravo, G., Bose, P., Alvarado, Y., Daver, N., Ravandi, F., Borthakur, G., Takahashi, K., Andreeff, M., Cortes, J., DiNardo, C., Jabbour, E.J., Kadia, T., Kornblau, S., Ohanian, M., Alfonso, A., Huang, X., Nogueras Gonzalez, G., Bodden, K., Pierce, S., Bueso-Ramos, C., Kantarjian, H., Garcia-Manero, G., 2017. Updated results from phase 2 study of guadecitabine for patients with untreated int-2/high risk myelodysplastic syndromes or chronic myelomonocytic leukemia. Haematologica 102 99-99.
Montalban-Bravo, G., Bose, P., Alvarado, Y., Daver, N., Ravandi, F., Borthakur, G., Takahashi, K., Andreeff, M., Cortes, J.E., DiNardo, C.D., Jabbour, E., Kadia, T.M., Kornblau, S.M., Ohanian, M., Pierola, A.A., Huang, X., Nogueras-Gonzalez, G.M., Bodden, K., Littles, K., Pierce, S., Bueso-Ramos, C.E., Kantarjian, H.M., Garcia-Manero, G., 2016. Initial results of a phase 2 study of guadecitabine (SGI-110), a novel subcutaneous (sc) hypomethylating agent, for patients with previously untreated intermediate-2 or high risk myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML). Blood 128.
Moreau, P., Facon, T., Touzeau, C., Benboubker, L., Delain, M., Badamo-Dotzis, J., Phelps, C., Doty, C., Smit, H., Fourneau, N., Forslund, A., Hellemans, P., Leleu, X., 2016. Quisinostat, bortezomib, and dexamethasone combination therapy for relapsed multiple myeloma. Leuk. Lymphoma 57, 1546–1559.
Morfouace, M., Nimmervoll, B., Boulos, N., Patel, Y.T., Shelat, A., Freeman III, B.B., Robinson, G.W., Wright, K., Gajjar, A., Stewart, C.F., Gilbertson, R.J., Roussel, M.F., 2016. Preclinical studies of 5-fluoro-2 '-deoxycytidine and tetrahydrouridine in pediatric brain tumors. J. Neuro Oncol. 126, 225–234.
Murakami, K., Miyagishi, M., 2014. Tiny masking locked nucleic acids effectively bind to mRNA and inhibit binding of microRNAs in relation to thermodynamic stability. Biomed Rep 2, 509–512.
Nakamae, S., Toba, Y., Takayama, K., Sakurai, F., Mizuguchi, H., 2018. Nanaomycin a treatment promotes hepatoblast differentiation from human iPS cells. Stem Cell. Dev. 27, 405–414.
Nakamura, K., Aizawa, K., Aung, K.H., Yamauchi, J., Tanoue, A., 2017. Zebularine up-regulates expression of CYP genes through inhibition of DNMT1 and PKR in HepG2 cells. Sci Rep-Uk 7.
Nandakumar, V., Vaid, M., Katiyar, S.K., 2011. (-)-Epigallocatechin-3-gallate reactivates silenced tumor suppressor genes, Cip1/p21 and p16(INK4a), by reducing DNA methylation and increasing histones acetylation in human skin cancer cells. Carcinogenesis 32, 537–544.
Norouzi, S., Majeed, M., Pirro, M., Generali, D., Sahebkar, A., 2018. Curcumin as an adjunct therapy and microRNA modulator in breast cancer. Curr. Pharmaceut. Des. 24, 171–177.
Obad, S., dos Santos, C.O., Petri, A., Heidenblad, M., Broom, O., Ruse, C., Fu, C.X., Lindow, M., Stenvang, J., Straarup, E.M., Hansen, H.F., Koch, T., Pappin, D., Hannon, G.J., Kauppinen, S., 2011. Silencing of microRNA families by seed-targeting tiny LNAs. Nat. Genet. 43 371-U160.

Ohno, M., Shibata, C., Kishikawa, T., Yoshikawa, T., Takata, A., Kojima, K., Akanuma, M., Kang, Y.J., Yoshida, H., Otsuka, M., Koike, K., 2013. The flavonoid apigenin improves glucose tolerance through inhibition of microRNA maturation in miRNA103 transgenic mice. Sci Rep-Uk 3.
Ohtsuka, M., Ling, H., Doki, Y., Mori, M., Calin, G.A., 2015. MicroRNA processing and human cancer. J. Clin. Med. 4, 1651–1667.
Omidian, K., Rafiei, H., Bandy, B., 2017. Polyphenol inhibition of benzo a pyrene-induced oxidative stress and neoplastic transformation in an in vitro model of carcinogenesis. Food Chem. Toxicol. 106, 165–174.
Onishi, M., Chiuzan, C., Fasano, J., Crew, K., Accordino, M., Tiersten, A., Shapiro, C., Jarpe, M., Qualye, S., Trede, N., Wheeler, C., Hershman, D., Silva, J., Maurer, M., Kalinksy, K., 2017. Multi-center phase IB trial of ACY-1215 (Ricolinostat) combined with nab-paclitaxel in unresectable or metastatic breast cancer. Cancer Res. 77, 2.
Osman, A.G., Chittiboyina, A.G., Khan, I.A., 2017. Cytoprotective role of dietary phytochemicals against cancer development via induction of phase II and antioxidant enzymes. In: In: Fishbein, J.C., Heilman, J.M. (Eds.), Advances in Molecular Toxicology 10. Academic Press Ltd-Elsevier Science Ltd, 24-28 Oval Road, London Nw1 7dx, Uk, pp. 99–137.
Ota, H., Tokunaga, E., Chang, K., Hikasa, M., Iijima, K., Eto, M., Kozaki, K., Akishita, M., Ouchi, Y., Kaneki, M., 2006. Sirt1 inhibitor, Sirtinol, induces senescence-like growth arrest with attenuated Ras-MAPK signaling in human cancer cells. Oncogene 25, 176–185.
Pan, F.P., Zhou, H.K., Bu, H.Q., Chen, Z.Q., Zhang, H., Xu, L.P., Tang, J., Yu, Q.J., Chu, Y.Q., Pan, J., Fei, Y., Lin, S.Z., Liu, D.L., Chen, L., 2016. Emodin enhances the demethylation by 5-Aza-CdR of pancreatic cancer cell tumor-suppressor genes P16, RASSF1A and ppENK. Oncol. Rep. 35, 1941–1949.
Pandey, A., Kulkarni, Y.A., Gaikwad, A.B., 2016. Curcumin: the Epigenetic Therapy. Elsevier Academic Press Inc, 525 B Street, Suite 1900, San Diego, Ca 92101-4495 USA.
Pandey, M., Kaur, P., Shukla, S., Abbas, A., Fu, P.F., Gupta, S., 2012. Plant flavone apigenin inhibits HDAC and remodels chromatin to induce growth arrest and apoptosis in human prostate cancer cells: in vitro and in vivo study. Mol. Carcinog. 51, 952–962.
Panuganti, S., Giammona, L.M., Kemper, J.M., Apostolidis, P., Lindsey, S., Papoutsakis, E., Miller, W.M., 2008. Nicotinamide increases the megakaryocytic maturation of human hematopoietic stem cells primarily due to SIRT inhibition. Blood 112, 850–851.
Paolini, A., Curti, V., Pasi, F., Mazzini, G., Nano, R., Capelli, E., 2015. Gallic acid exerts a protective or an anti-proliferative effect on glioma T98G cells via dose-dependent epigenetic regulation mediated by miRNAs. Int. J. Oncol. 46, 1491–1497.
Paredes-Gonzalez, X., Fuentes, F., Su, Z.Y., Kong, A.N.T., 2014. Apigenin reactivates Nrf2 anti-oxidative stress signaling in mouse skin epidermal JB6 P + cells through epigenetics modifications. AAPS J. 16, 727–735.
Park, J.E., Sun, Y., Lim, S.K., Tam, J.P., Dekker, M., Chen, H., Sze, S.K., 2017. Dietary phytochemical PEITC restricts tumor development via modulation of epigenetic writers and erasers. Sci Rep-Uk 7.
Pauer, L.R., Olivares, J., Cunningham, C., Williams, A., Grove, W., Kraker, G., Olson, S., Nemunaitis, J., 2004. Phase I study of oral CI-994 in combination with carboplatin and paclitaxel in the treatment of patients with advanced solid tumors. Canc. Invest. 22, 886–896.
Petropoulos, S., Di Gioia, F., Ntatsi, G., 2017. Vegetable organosulfur compounds and their health promoting effects. Curr. Pharmaceut. Des. 23, 2850–2875.
Plummer, R., Vidal, L., Griffin, M., Lesley, M., de Bono, J., Coulthard, S., Sludden, J., Siu, L.L., Chen, E.X., Oza, A.M., Reid, G.K., McLeod, A.R., Besterman, J.M., Lee, C., Judson, I., Calvert, H., Bloody, A.V., 2009. Phase I study of MG98, an oligonucleotide antisense inhibitor of human DNA methyltransferase 1, given as a 7-day infusion in patients with advanced solid tumors. Clin. Canc. Res. 15, 3177–3183.
Popat, R., Brown, S.R., Tillotson, A.-L., Collinson, F., Flanagan, L.M., Williams, C.D., Yong, K.L., Cook, G., Jenner, M.W., Kaiser, M., Cavet, J., El-Sharkawi, D., Ng, C.-H., Low, E., Morgan, G.J., Davies, F.E., 2016. A phase I dose-escalation study of the class 1 selective histone deacetylase inhibitor CHR-3996 in combination with tosedostat for patients with relapsed, refractory multiple myeloma: results of the muk three trial. Blood 128.
Portela, A., Esteller, M., 2010. Epigenetic modifications and human disease. Nat. Biotechnol. 28, 1057–1068.
Poschner, S., Maier-Salamon, A., Zehl, M., Wackerlig, J., Dobusch, D., Pachmann, B., Sterlini, K.L., Jaeger, W., 2017. The impacts of genistein and daidzein on estrogen conjugations in human breast cancer cells: a targeted metabolomics approach. Front. Pharmacol. 8.
Pratheeshkumar, P., Son, Y.O., Divya, S.P., Wang, L., Turcios, L., Roy, R.V., Hitron, J.A., Kim, D., Dai, J., Asha, P., Zhang, Z., Shi, X.L., 2017. Quercetin inhibits Cr(VI)-induced malignant cell transformation by targeting miR-21-PDCD4 signaling pathway. Oncotarget 8, 52118–52131.
Priyadarsini, R.V., Vinothini, G., Murugan, R.S., Manikandan, P., Nagini, S., 2011. The flavonoid quercetin modulates the hallmark capabilities of hamster buccal pouch tumors. Nutr. Canc. 63, 218–226.
Qian, B.-J., Tian, C.-C., Ling, X.-H., Yu, L.-L., Ding, F.-Y., Huo, J.-H., Zhu, L.-C., Wen, Y.-L., Zhang, J.-H., Jing, P., 2018a. miRNA-150-5p associate with antihypertensive effect of epigallocatechin-3-gallate revealed by aorta miRNome analysis of spontaneously hypertensive rat. Life Sci. 203, 193–202.
Qian, Y.Y., Liu, Z.S., Zhang, Z.D., Levenson, A.S., Li, K., 2018b. Pterostilbene increases PTEN expression through the targeted downregulation of microRNA-19a in hepatocellular carcinoma. Mol. Med. Rep. 17, 5193–5201.
Qiao, Y.J., Xu, L.N., Tao, X.F., Yin, L.H., Qi, Y., Xu, Y.W., Han, X., Tang, Z.Y., Ma, X.D., Liu, K.X., Peng, J.Y., 2018. Protective effects of dioscin against fructose-induced renal damage via adjusting Sirt3-mediated oxidative stress, fibrosis, lipid metabolism and inflammation. Toxicol. Lett. 284, 37–45.
Qin, J., Chen, J.X., Zhu, Z., Teng, J.A., 2015. Genistein inhibits human colorectal cancer growth and suppresses MiR-95, akt and SGK1. Cell. Physiol. Biochem. 35, 2069–2077.
Qin, W.Y., Zhang, K., Clarke, K., Weiland, T., Sauter, E.R., 2014. Methylation and miRNA effects of resveratrol on mammary tumors vs. Normal tissue. Nutr. Canc. 66, 270–277.
Qiu, X.Y., Xiao, X., Li, N., Li, Y.M., 2017. Histone deacetylases inhibitors (HDACis) as novel therapeutic application in various clinical diseases. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 72, 60–72.
Querfeld, C., Foss, F.M., Pinter-Brown, L.C., Porcu, P., William, B.M., Pacheco, T., Haverkos, B.M., Kim, Y.H., Guitart, J., Halwani, A.S., DeSimone, J., Seto, A.G., Pestano, L.A., Jackson, A.L., Williams, P.J., Dickinson, B.A., Ruckman, J., Gordon, G., Rubin, P., Marshall, B.S., 2017. Phase 1 study of the safety and efficacy of MRG-106, a synthetic inhibitor of microRNA-155, in CTCL patients. Blood 130.
Raje, N., Hari, P.N., Vogl, D.T., Jagannath, S., Orlowski, R.Z., Supko, J.G., Stephenson, J., Jones, S.S., Wheeler, C., Lonial, S., 2012. Rocilinostat (ACY-1215), a selective HDAC6 inhibitor, alone and in combination with bortezomib in multiple myeloma: preliminary results from the first-in-humans phase I/II study. Blood 120.
Regna, N.L., Chafin, C.B., Hammond, S.E., Puthiyaveetil, A.G., Caudell, D.L., Reilly, C.M., 2014. Class I and II histone deacetylase inhibition by ITF2357 reduces SLE pathogenesis in vivo. Clin. Immunol. 151, 29–42.
Reilmann, R., Squitieri, F., Priller, J., Saft, C., Mariotti, C., Suessmuth, S.D., Nemeth, A.H., Tabrizi, S.J., Quarrell, O., Craufurd, D., Rickards, H., Rosser, A., Darpo, B., Tessari, M., Szynol, A., Fischer, D.F., Frost, C., Farmer, R.E., Landwehrmeyer, G.B., Westerberg, G., 2014. Safety and tolerability of selisistat for the treatment of huntington's disease: results from a randomised, double-blind, placebo-controlled phase ii trial. J. Neurol. Neurosurg. Psychiatry 85 A102-A102.
Reu, F.J., Maitra, R.K., Rempinski, D.R., Bae, S.I., Beaulieu, N., Macleod, A.R., Borden, E.C., 2005. Reactivation of the tumor suppressor RASSF1A by selective depletion of DNA methyltransferase 1 (DNMT1) by MG98 sensitizes renal cancer cells to interferon (IFN)-induced apoptosis. J. Clin. Oncol. 23 847S-847S.
Roh, M.S., Kim, C.W., Park, B.S., Kim, G.C., Jeong, J.H., Kwon, H.C., Suh, D.J., Cho, K.H., Yee, S.B., Yoo, Y.H., 2004. Mechanism of histone deacetylase inhibitor Trichostatin A induced apoptosis in human osteosarcoma cells. Apoptosis 9, 583–589.
Rowinsky, E.K., de Bono, J., Deangelo, D.J., van Oosterom, A., Morganroth, J., Laird, G.H., Dugan, M., Scott, J.W., Ottmann, O.G., 2005. Cardiac monitoring in phase I trials of a novel histone deacetylase (HDAC) inhibitor LAQ824 in patients with advanced solid tumors and hematologic malignancies. J. Clin. Oncol. 23 224S-224S.
Royston, K.J., Udayakumar, N., Lewis, K., Tollefsbol, T.O., 2017. A novel combination of withaferin a and sulforaphane inhibits epigenetic machinery, cellular viability and induces apoptosis of breast cancer cells. Int. J. Mol. Sci. 18, 17.
Rupaimoole, R., Slack, F.J., 2017. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat. Rev. Drug Discov. 16, 203–221.
Russo, M., Spagnuolo, C., Russo, G.L., Skalicka-Wozniak, K., Daglia, M., Sobarzo-Sanchez, E., Nabavi, S.F., Nabavi, S.M., 2018. Nrf2 targeting by sulforaphane: a potential therapy for cancer treatment. Crit. Rev. Food Sci. Nutr. 58, 1391–1405.
Sanchez, H., Hossain, M.B., Lera, L., Hirsch, S., Albala, C., Uauy, R., Broberg, K., Ronco, A.M., 2017. High levels of circulating folate concentrations are associated with DNA methylation of tumor suppressor and repair genes p16, MLH1, and MGMT in elderly Chileans. Clin. Epigenet. 9.
Savino, A.M., Sarno, J., Trentin, L., Vieri, M., Fazio, G., Bardini, M., Bugarin, C., Fossati, G., Davis, K.L., Gaipa, G., Izraeli, S., Meyer, L.H., Nolan, G.P., Biondi, A., Te Kronnie, G., Palmi, C., Cazzaniga, G., 2017. The histone deacetylase inhibitor givinostat (ITF2357) exhibits potent anti-tumor activity against CRLF2-rearranged BCP-ALL. Leukemia 31, 2365–2375.
Sharma, V., Kumar, L., Mohanty, S.K., Maikhuri, J.P., Rajender, S., Gupta, G., 2016. Sensitization of androgen refractory prostate cancer cells to anti androgens through re-expression of epigenetically repressed androgen receptor - synergistic action of quercetin and curcumin. Mol. Cell. Endocrinol. 431, 12–23.
Shi, X., Zheng, C., Li, C., Hou, K., Wang, X., Yang, Z., Liu, C., Liu, Y., Che, X., Qu, X., 2018. 4-Phenybutyric acid promotes gastric cancer cell migration via histone deacetylase inhibition-mediated HER3/HER4 up-regulation. Cell Biol. Int. 42, 53–62.
Shibata, C., Ohno, M., Otsuka, M., Kishikawa, T., Goto, K., Muroyama, R., Kato, N., Yoshikawa, T., Takata, A., Koike, K., 2014. The flavonoid apigenin inhibits hepatitis C virus replication by decreasing mature microRNA122 levels. Virology 462, 42–48.
Shih, C.C., Liao, M.H., Hsiao, T.S., Hii, H.P., Shen, C.H., Chen, S.J., Ka, S.M., Chang, Y.L., Wu, C.C., 2016. Procainamide inhibits DNA methylation and alleviates multiple organ dysfunction in rats with endotoxic shock. PloS One 11, 24.
Shu, L.M., Khor, T.O., Lee, J.H., Boyanapalli, S.S.S., Huang, Y., Wu, T.Y., Saw, C.L.L., Cheung, K.L., Kong, A.N.T., 2011. Epigenetic CpG demethylation of the promoter and reactivation of the expression of neurog1 by curcumin in prostate LNCaP cells. AAPS J. 13, 606–614.
Shukla, S., Meeran, S.M., Katiyar, S.K., 2014. Epigenetic regulation by selected dietary phytochemicals in cancer chemoprevention. Cancer Lett. 355, 9–17.
Singh, V., Sharma, P., Capalash, N., 2013. DNA methyltransferase-1 inhibitors as epigenetic therapy for cancer. Curr. Cancer Drug Targets 13, 379–399.
Sivaraj, D., Green, M.M., Gasparetto, C., 2017. Panobinostat for the management of multiple myeloma. Future Oncol. 13, 477–488.
Song, K.J., Lv, T., Chen, Y.L., Diao, Y.C., Yao, Q., Wang, Y.K., 2018. Emodin inhibits TGF-2 by activating the FOXD3/miR-199a axis in ovarian cancer cells in vitro. Oncol. Rep. 39, 2063–2070.
Song, Y., Hai, T., Wang, Y., Guo, R., Li, W., Wang, L., Zhou, Q., 2014. Epigenetic reprogramming, gene expression and in vitro development of porcine SCNT embryos are significantly improved by a histone deacetylase inhibitor-m-carboxycinnamic acid bishydroxamide (CBHA). Protein Cell 5, 382–393.

Spurgeon, S., Sharma, K., Claxton, D.F., Ehmann, C., Shimko, S., Stewart, A., Parekh, S., Leshchenko, V.V., Chen, Y.Y., Mori, M., Pu, J.J., Epner, E., 2014. Final results of a phase 1-2 study of vorinostat (SAHA), cladribine, and rituximab (SCR) relapsed B-cell non-hodgkin's lymphoma and previously untreated mantle cell lymphoma. Blood 124, 4.

Starlard-Davenport, A., Kutanzi, K., Tryndyak, V., Word, B., Lyn-Cook, B., 2013. Restoration of the methylation status of hypermethylated gene promoters by microRNA-29b in human breast cancer: a novel epigenetic therapeutic approach. J carcinogen 12 15-15.

Sun, L.P., Chen, A.L., Hung, H.C., Chien, Y.H., Huang, J.S., Huang, C.Y., Chen, Y.W., Chen, C.N., 2012. Chrysin: a histone deacetylase 8 inhibitor with anticancer activity and a suitable candidate for the standardization of Chinese propolis. J. Agric. Food Chem. 60, 11748–11758.

Sundaram, M.K., Ansari, M.Z., Mutery, A.A., Ashraf, M., Nasab, R., Rai, S., Rais, N., Hussain, A., 2017. Genistein induces alterations of epigenetic modulatory signatures in human cervical cancer cells. Anti-Cancer Agent Me 18, 412.

Takahashi, K., Abaza, Y., Atallah, E.L., Medeiros, B.C., Khal, S., Arellano, M.L., Patnaik, M., Ghalie, R., Garcia-Manero, G., 2017. Correlation between mutation clearance and clinical response in elderly patients with acute myeloid leukemia (AML) treated with azacitidine and pracinostat. J. Clin. Oncol. 35, 5.

Takai, N., Ueda, T., Nishida, M., Nasu, K., Matsuda, K., Kusumoto, M., Narahara, H., 2015. CBHA is a family of hybrid polar compounds that inhibit histone deacetylase, and induces growth inhibition, cell cycle arrest and apoptosis in human endometrial and ovarian cancer cells (Retraction of vol 70, pg 97, 2006). Oncology 88 320-320.

Takemura, Y., Satoh, M., Hatanaka, K., Kubota, S., 2018. Zebularine exerts its anti-proliferative activity through S phase delay and cell death in human malignant mesothelioma cells. Biosci. Biotechnol. Biochem. 1–6.

Tao, H., Shi, K.-H., Yang, J.-J., Huang, C., Zhan, H.-Y., Li, J., 2014. Histone deacetylases in cardiac fibrosis: current perspectives for therapy. Cell. Signal. 26, 521–527.

Taverna, P., Scholl, J., Shi, C., Oganesian, A., Redkar, S., Azab, M., 2012. SGI-110, a novel subcutaneous (SQ) second generation DNA hypomethylating agent achieves improved pharmacodynamics (PD), safety and pharmacokinetics (PK) in comparison to IV decitabine in a non-human primate in vivo study. Cancer Res. 72.

Thomson, D.W., Dinger, M.E., 2016. Endogenous microRNA sponges: evidence and controversy. Nat. Rev. Genet. 17, 272–283.

Toden, S., Tran, H.M., Tovar-Camargo, O.A., Okugawa, Y., Goel, A., 2016. Epigallocatechin-3-gallate targets cancer stem-like cells and enhances 5-fluorouracil chemosensitivity in colorectal cancer. Oncotarget 7, 16158–16171.

Tollefsbol, T.O., 2012. Epigenetics of Human Disease.

Trang, P., Wiggins, J.F., Daige, C.L., Cho, C., Omotola, M., Brown, D., Weidhaas, J.B., Bader, A.G., Slack, F.J., 2011. Systemic delivery of tumor suppressor microRNA mimics using a neutral lipid emulsion inhibits lung tumors in mice. Mol. Ther. 19, 1116–1122.

Trevino-Saldana, N., Garcia-Rivas, G., 2017. Regulation of sirtuin-mediated protein deacetylation by cardioprotective phytochemicals. Oxid Med Cell Longev 88.

Tseng, T.H., Chien, M.H., Lin, W.L., Wen, Y.C., Chow, J.M., Chen, C.K., Kuo, T.C., Lee, W.J., 2017. Inhibition of MDA-MB-231 breast cancer cell proliferation and tumor growth by apigenin through induction of G2/M arrest and histone H3 acetylation-mediated p21(WAF1/CIP1) expression. Environ. Toxicol. 32, 434–444.

Tu, F., Pang, Q., Huang, T., Zhao, Y., Liu, M., Chen, X., 2017. Apigenin ameliorates post-stroke cognitive deficits in rats through histone acetylation-mediated neurochemical alterations. Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. 23, 4004–4013.

van der Ree, M.H., de Vree, J.M., Stelma, F., Willemse, S., van der Valk, M., Rietdijk, S., Molenkamp, R., Schinkel, J., van Nuenen, A., Beuers, U., Hadi, S., Harbers, M., van der Veer, E., Liu, K., Grundy, J., Patick, A.K., Pavlicek, A., Blem, J., Huang, M., Grint, P., Neben, S., Gibson, N.W., Kootstra, N.A., Reesink, H.W., 2017. Safety, tolerability, and antiviral effect of RG-101 in patients with chronic hepatitis C: a phase 1B, double-blind, randomised controlled trial. Lancet 389, 709–717.

van der Ree, M.H., van der Meer, A.J., van Nuenen, A.C., de Bruijne, J., Ottosen, S., Janssen, H.L., Kootstra, N.A., Reesink, H.W., 2016. Miravirsen dosing in chronic hepatitis C patients results in decreased microRNA-122 levels without affecting other microRNAs in plasma. Aliment. Pharmacol. Ther. 43, 102–113.

van Zandwijk, N., Pavlakis, N., Kao, S., Clarke, S., Lee, A., Brahmbhatt, H., Macdiarmid, J., Pattison, S., Leslie, F., Huynh, Y., Linton, A., Reid, G., 2015. Mesomir 1: a phase i study of targomirs in patients with refractory malignant pleural mesothelioma (MPM) and lung cancer (NSCLC). Ann. Oncol. 26 16-16.

Veeranki, O.L., Bhattacharya, A., Tang, L., Marshall, J.R., Zhang, Y., 2015. Cruciferous vegetables, isothiocyanates, and prevention of bladder cancer. Curr Pharm Rep 1, 272–282.

Venturelli, S., Berger, A., Bocker, A., Busch, C., Weiland, T., Noor, S., Leischner, C., Schleicher, S., Mayer, M., Weiss, T.S., Bischoff, S.C., Lauer, U.M., Bitzer, M., 2013. Resveratrol as a Pan-HDAC inhibitor alters the acetylation status of jistone proteins in human-derived hepatoblastoma cells. PloS One 8.

Vey, N., Prebet, T., Thalamas, C., Charbonnier, A., Rey, J., Kloos, I., Liu, E., Luan, Y., Vezan, R., Graef, T., Recher, C., 2017. Phase 1 dose-escalation study of oral abexinostat for the treatment of patients with relapsed/refractory higher-risk myelodysplastic syndromes, acute myeloid leukemia, or acute lymphoblastic leukemia. Leuk. Lymphoma 58, 1880–1886.

Vitfell-Rasmussen, J., Lind-Hansen, M., Safwat, A., Rossen, P., Knoblauch, P., Jones, R.L., Judson, I.R., Krarup-Hansen, A., 2015. A phase I/II clinical trial of belinostat (PXD101) in combination with doxorubicin in patients with soft tissue sarcomas (STS). J. Clin. Oncol. 33.

Wagner, B., Tran, P., Pagarigan, R., Neben, S., Kim, J., Zarrouki, B., Andersson, P., Lindstedt, E.L., Turnbull, A., MacKenna, D., 2015. RG-125 (AZD4076): clinical candidate with a novel modality to treat insulin resistance through inhibiting miR-103/107. Diabetologia 58 S396-S396.

Wahlgren, J., Statello, L., Skogberg, G., Telemo, E., Valadi, H., 2016. Delivery of small interfering RNAs to cells via exosomes. In: Shum, K., Rossi, J. (Eds.), SiRNA Delivery Methods: Methods and Protocols, pp. 105–125.

Walewski, J., Paszkiewicz-Kozik, E., Warszewska, A., Borsaru, G., Moicean, A., Hellmann, A., Mayer, J., Hauns, B., Mais, A., Henning, S.W., Hentsch, B., 2011. Final results of the phase II SAPHIRE trial of resminostat (4SC-201) in patients with relapsed/refractory hodgkin lymphoma. Blood 118 1149-1149.

Wallace, G.C., Haar, C.P., Vandergrift, W.A., Giglio, P., Dixon-Mah, Y.N., Varma, A.K., Ray, S.K., Patel, S.J., Banik, N.L., Das, A., 2013. Multi-targeted DATS prevents tumor progression and promotes apoptosis in ectopic glioblastoma xenografts in SCID mice via HDAC inhibition. J. Neuro Oncol. 114, 43–50.

Wang, G.X., Dai, F., Yu, K., Jia, Z.F., Zhang, A.L., Huang, Q., Kang, C.S., Jiang, H., Pu, P.Y., 2015. Resveratrol inhibits glioma cell growth via targeting oncogenic microRNAs and multiple signaling pathways. Int. J. Oncol. 46, 1739–1747.

Wang, H., Bian, S.J., Yang, C.S., 2011. Green tea polyphenol EGCG suppresses lung cancer cell growth through upregulating miR-210 expression caused by stabilizing HIF-1 alpha. Carcinogenesis 32, 1881–1889.

Wang, J.Y., Liu, X.F., Wu, H.C., Ni, P.H., Gu, Z.D., Qiao, Y.X., Chen, N., Sun, F.Y., Fan, Q.S., 2010. CREB up-regulates long non-coding RNA, HULC expression through interaction with microRNA-372 in liver cancer. Nucleic Acids Res. 38, 5366–5383.

Wang, S.W., Yan-Neale, Y., Cai, R., Alimov, I., Cohen, D., 2006. Activation of mitochondrial pathway is crucial for tumor selective induction of apoptosis by LAQ824. Cell Cycle 5, 1662–1668.

Wang, X.Z., Cheng, Y., Wang, K.L., Liu, R., Yang, X.L., Wen, H.M., Chai, C., Liang, J.Y., Wu, H., 2016a. Peperomin E reactivates silenced tumor suppressor genes in lung cancer cells by inhibition of DNA methyltransferase. Cancer Sci. 107, 1506–1519.

Wang, Y.L., Liui, H.L., Fu, R.G., Wang, Z.W., Ren, H.T., Dai, Z.J., Jing, Y.Y., Li, Y., 2016b. HDAC inhibitor oxamflatin induces morphological changes and has strong cytostatic effects in ovarian cancer cell lines. Curr. Mol. Med. 16, 232–242.

Wang, Z., 2011. The principles of MiRNA-masking antisense oligonucleotides technology. In: Wu, W. (Ed.), MicroRNA and Cancer: Methods and Protocols, pp. 43–49.

Wei, D., Yang, L.Y., Lv, B., Chen, L.J., 2017. Genistein suppresses retinoblastoma cell viability and growth and induces apoptosis by upregulating miR-145 and inhibiting its target ABCE1. Mol. Vis. 23, 385–394.

Weng, Y.P., Hung, P.F., Ku, W.Y., Chang, C.Y., Wu, B.H., Wu, M.H., Yao, J.Y., Yang, J.R., Lee, C.H., 2018. The inhibitory activity of gallic acid against DNA methylation: application of gallic acid on epigenetic therapy of human cancers. Oncotarget 9, 361–374.

Winquist, E., Knox, J., Ayoub, J.P., Wood, L., Wainman, N., Reid, G.K., Pearce, L., Shah, A., Eisenhauer, E., 2006. Phase II trial of DNA methyltransferase 1 inhibition with the antisense oligonucleotide MG98 in patients with metastatic renal carcinoma: a National Cancer Institute of Canada Clinical Trials Group investigational new drug study. Invest. N. Drugs 24, 159–167.

Wu, F., Wang, J., Sun, J., Shen, L., Liu, M., Zhao, E., 2018. Procaine stimulates aquaporin-5 expression in human salivary gland ductal cells via the suppression of DNA methyltransferase-1. Mol. Med. Rep. 17, 7996–8002.

Wu, F.F., Cui, L.Y., 2017. Resveratrol suppresses melanoma by inhibiting NF-kappa B/miR-221 and inducing TFG expression. Arch. Dermatol. Res. 309, 823–831.

Xie, H.J., Ren, X.L., Xin, S.N., Lan, X.L., Lu, G.F., Lin, Y., Yang, S.S., Zeng, Z.C., Liao, W.T., Ding, Y.Q., Liang, L., 2016. Emerging roles of circRNA_001569 targeting miR-145 in the proliferation and invasion of colorectal cancer. Oncotarget 7, 26680–26691.

Xu, J.N., Sun, J.J., Wang, P.C., Ma, X.C., Li, S., 2018. Pendant HDAC inhibitor SAHA derivatised polymer as a novel prodrug micellar Carrier for anticancer drugs. J. Drug Target. 26, 448–457.

Yamada, S., Tsukamoto, S., Huang, Y., Makio, A., Kumazoe, M., Yamashita, S., Tachibana, H., 2016. Epigallocatechin-3-O-gallate up-regulates microRNA-let-7b expression by activating 67-kDa laminin receptor signaling in melanoma cells. Sci Rep-Uk 6.

Yang, H., Liu, P., Zhang, J., Peng, X., Lu, Z., Yu, S., Meng, Y., Tong, W.M., Chen, J., 2016. Long noncoding RNA MIR31HG exhibits oncogenic property in pancreatic ductal adenocarcinoma and is negatively regulated by miR-193b. Oncogene 35, 3647–3657.

Yang, L., Hou, J., Cui, X.H., Suo, L.N., Lv, Y.W., 2017a. RG108 induces the apoptosis of endometrial cancer Ishikawa cell lines by inhibiting the expression of DNMT3B and demethylation of HMLH1. Eur Rev Med Pharmaco 21, 5056–5064.

Yang, X.X., Tang, X.L., Sun, P., Shi, Y.J., Liu, K., Hassan, S.H., Stetler, R.A., Chen, J., Yin, K.J., 2017b. MicroRNA-15a/16-1 antagomir ameliorates ischemic brain injury in experimental stroke. Stroke 48, 1941 -+.

Yang, Y., Jin, Z., Dong, R., Zheng, C., Huang, Y., Zheng, Y., Shen, Z., Chen, G., Luo, X., Zheng, S., 2018. MicroRNA-29b/142-5p contribute to the pathogenesis of biliary atresia by regulating the IFN-gamma gene. Cell Death Dis. 9.

Yao, R.S., Han, D.Y., Sun, X.Y., Xie, Y., Wu, Q.Y., Fu, C.L., Yao, Y., Li, H.J., Li, Z.Y., Xu, K.L., 2018. Scriptaid inhibits cell survival, cell cycle, and promotes apoptosis in multiple myeloma via epigenetic regulation of p21. Exp. Hematol. 60, 63–72.

Yi, L., Su, Q., 2013. Molecular mechanisms for the anti-cancer effects of diallyl disulfide. Food Chem. Toxicol. 57, 362–370.

Younes, A., Hernandez, F., Bociek, R.G., Kasamon, Y.L., Lee, P., Gore, L., Copeland, A.R., 2011a. The HDAC inhibitor entinostat (SNDX-275) induces clinical responses in patients with relapsed and refractory hodgkin's lymphoma: results of ENGAGE-501 multicenter phase 2 study. Blood 118 1168-1168.

Younes, A., Oki, Y., Bociek, R.G., Kuruvilla, J., Fanale, M., Neelapu, S., Copeland, A., Buglio, D., Galal, A., Besterman, J., Li, Z., Drouin, M., Patterson, T., Ward, M.R., Paulus, J.K., Ji, Y., Medeiros, L.J., Martell, R.E., 2011b. Mocetinostat for relapsed classical Hodgkin's lymphoma: an open-label, single-arm, phase 2 trial. Lancet Oncol. 12, 1222–1228.

Yu, C.G., Gong, A.Y., Chen, D.Q., Leon, D.S., Young, C.Y.F., Chen, X.M., 2013a. Phenethyl isothiocyanate inhibits androgen receptor-regulated transcriptional activity in prostate cancer cells through suppressing PCAF. Mol. Nutr. Food Res. 57, 1825–1833.

Yu, J.H., Peng, Y., Wu, L.C., Xie, Z.L., Deng, Y.C., Hughes, T., He, S., Mo, X.K., Chiu, M., Wang, Q.E., He, X.M., Liu, S.J., Grever, M.R., Chan, K.K., Liu, Z.F., 2013b. Curcumin down-regulates DNA methyltransferase 1 and plays an anti-leukemic role in acute myeloid leukemia. PloS One 8.

Zaman, M.S., Shahryari, V., Deng, G.R., Thamminana, S., Saini, S., Majid, S., Chang, I., Hirata, H., Ueno, K., Yamamura, S., Singh, K., Tanaka, Y., Tabatabai, Z.L., Dahiya, R., 2012. Up-regulation of MicroRNA-21 correlates with lower kidney cancer survival. PloS One 7.

Zhang, C.Y., Shu, L.M., Kim, H., Khor, T.O., Wu, R.Y., Li, W.J., Kong, A.N.T., 2016. Phenethyl isothiocyanate (PEITC) suppresses prostate cancer cell invasion epigenetically through regulating microRNA-194. Mol. Nutr. Food Res. 60, 1427–1436.

Zhang, C.Y., Su, Z.Y., Khor, T.O., Shu, L.M., Kong, A.N.T., 2013. Sulforaphane enhances Nrf2 expression in prostate cancer TRAMP C1 cells through epigenetic regulation. Biochem. Pharmacol. 85, 1398–1404.

Zhang, H., Shang, Y.-P., Chen, H.-y., Li, J., 2017a. Histone deacetylases function as novel potential therapeutic targets for cancer. Hepatol. Res. 47, 149–159.

Zhang, J., Lai, Z., Huang, W., Ling, H., Lin, M., Tang, S., Liu, Y., Tao, Y., 2017b. Apicidin inhibited proliferation and invasion and induced apoptosis via mitochondrial pathway in non-small cell lung cancer GLC-82 cells. Anti-Cancer Agent Me 17, 1374–1382.

Zhang, S.Q., al-Maghout, T., Bissinger, R., Zeng, N., Pelzl, L., Salker, M.S., Cheng, A.C., Singh, Y., Lang, F., 2017c. Epigallocatechin-3-gallate (EGCG) up-regulates miR-15b expression thus attenuating store operated calcium entry (SOCE) into murine CD4(+) T cells and human leukaemic T cell lymphoblasts. Oncotarget 8, 89500–89514.

Zhou, C.X., Ding, J., Wu, Y.W., 2014a. Resveratrol induces apoptosis of bladder cancer cells via miR-21 regulation of the Akt/Bcl-2 signaling pathway. Mol. Med. Rep. 9, 1467–1473.

Zhou, W., Wang, S.Q., Ying, Y., Zhou, R.Q., Mao, P., 2017. miR-196b/miR-1290 participate in the antitumor effect of resveratrol via regulation of IGFBP3 expression in acute lymphoblastic leukemia. Oncol. Rep. 37, 1075–1083.

Zhou, X.M., Zhang, X., Zhang, X.S., Zhuang, Z., Li, W., Sun, Q., Li, T., Wang, C.X., Zhu, L., Shi, J.X., Zhou, M.L., 2014b. SIRT1 inhibition by sirtinol aggravates brain edema after experimental subarachnoid hemorrhage. J. Neurosci. Res. 92, 714–722.

Zhu, K.W., Wang, W.C., 2016. Green tea polyphenol EGCG suppresses osteosarcoma cell growth through upregulating miR-1. Tumor Biol. 37, 4373–4382.

Zhu, L.C., Wu, K., Ma, S.L., Zhang, S.R., 2015. HDAC inhibitors: a new radiosensitizer for non-small-cell lung cancer. Tumori 101, 257–262.