BBA - Molecular Basis of Disease 1868 (2022) 166552

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

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

Review

Novel epigenetic therapeutic strategies and targets in cancer

Quratulain Babar [a], Ayesha Saeed [a], Tanveer A. Tabish [b,*], Sabrina Pricl [c], Helen Townley [d], Nanasaheb Thorat [d,*]

[a] Department of Biochemistry Government College University, Faisalabad, Pakistan
[b] Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford OX3 7BN, United Kingdom
[c] MolBNL@UniTS-DEA, University of Trieste, Piazzale Europa 1, 34127 Trieste, Italy
[d] Nuffield Department of Women's and Reproductive Health, John Radcliffe Hospital, Medical Sciences Division, University of Oxford, Oxford OX3 9DU, United Kingdom

ARTICLE INFO

Keywords:
Epigenetics
Therapeutic targets
cancer
Nanomedicines

ABSTRACT

The critical role of dysregulated epigenetic pathways in cancer genesis, development, and therapy has typically been established as a result of scientific and technical innovations in next generation sequencing. RNA interference, histone modification, DNA methylation and chromatin remodelling are epigenetic processes that control gene expression without causing mutations in the DNA. Although epigenetic abnormalities are thought to be a symptom of cell tumorigenesis and malignant events that impact tumor growth and drug resistance, physicians believe that related processes might be a key therapeutic target for cancer treatment and prevention due to the reversible nature of these processes. A plethora of novel strategies for addressing epigenetics in cancer therapy for immuno-oncological complications are currently available - ranging from basic treatment to epigenetic editing. – and they will be the subject of this comprehensive review. In this review, we cover most of the advancements made in the field of targeting epigenetics with special emphasis on microbiology, plasma science, biophysics, pharmacology, molecular biology, phytochemistry, and nanoscience.

1. Introduction: epigenetic therapeutics in cancer

Either with aging, or cancer malignancies, our DNA undergoes genetic and epigenetic alterations which in turn result in altered gene expression. Modified gene expression result in loss of histones, imbalance of repressive and activating modifications, evasion and expansion in heterochromatin, transcriptional changes, and breakdown of nuclear lamina along with chromatin remodelling [1–5]. Epigenetic modifications including DNA methylation, histone modifications, microRNAs, and nucleosome remodelling regulate gene expression in human malignancies (as shown in Fig. 1). A further demonstration of the genetics/epigenetics relationship in cancer is the presence of abnormal metabolism and biochemical pathways, as well as mutation in genes that are epigenetic actors in cancer pathologies [6].

Due to the reversible nature of epigenetic alterations in cancer, their timely targeting has emerged as a fascinating option in cancer therapeutics [7]. Many drugs have been developed which specifically target proteins that regulate histone acetylation and DNA methylation [8]. Some of these proteins are already being tested in clinical trials with encouraging results, highlighting the potential of epigenetic therapy and paving the way for the development of innovative drugs targeting epigenetic pathways in cancer [9]. Both the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved the clinical use of two DNA demethylating agents, decitabine (Dacogen®) and azacytidine (Vidaza®, Azadine®, Onureg®), for their potential efficacies in haematological malignancies and myelodysplastic syndromes (MDS) [10].

Both compounds are chemical analogues of the cytidine nucleoside and must be integrated into DNA to exert their effect. After being produced as anti-metabolites in the 1960s [11,12], they were discovered to have DNA-targeted activity via inhibiting DNA methyltransferases (DNMTs). The significant toxicities associated with high drug doses in cancer patients have previously precluded their widespread use, especially in solid tumors [13]. Nonetheless, these compounds have regained considerable clinical attention over the recent years, the usage of low dose regimens showing promise in terms of clinical outcomes while causing mild side effects [14].

Many efforts have been undertaken to elucidate the processes by which decitabine and azacitidine exhibit therapeutic effectiveness [15]. These drugs have a variety of effects, including cancer cell

* Corresponding authors.
E-mail addresses: tanveer.tabish@cardiov.ox.ac.uk (T.A. Tabish), thoratnd@gmail.com (N. Thorat).

https://doi.org/10.1016/j.bbadis.2022.166552
Received 14 June 2022; Received in revised form 8 September 2022; Accepted 14 September 2022
Available online 17 September 2022

differentiation, DNA damage, the formation of covalent addition reactions between DNMTs and DNA with azanucleoside substitutions, immunological modulatory actions through cancer/germ-line protein reactivation, suppression of the NF-κB anti-apoptotic pathway, among others [10]. Notably, some data suggest that these drugs may alter gene expression independently of DNA methylation by disrupting complex protein interactions via the inhibition and removal of DNMTs from the nucleus [16,17]. Additionally, it has been hypothesized that the DNA methylation-dependent and -independent effects of these molecules may ultimately result in the reversal of genome-wide epigenetic alterations in cancer via multiple altered cell proliferation pathways followed by amplification of protooncogenes or the silencing of tumor suppressor genes [18]. Methylation is involved in several processes like cell cycle, differentiation, developmental and DNA repair that's why any alteration in this leads to disease. HDACi and DNMTs inhibitors downregulate all those genes which are involved in angiogenesis, migration, cell survival and epithelial to mesenchymal transition (EMT) while upregulate the expression of apoptotic genes [19]. Aside from the underlying mechanisms of action, studying phenomena involved in drug resistance could be significantly important for the translation of this modality into clinic [18]. For instance, it has been shown that high levels of cytosine deaminase and low levels of nucleoside transporters and/or of deoxycytidine kinase are hallmark of imparting resistance to decitabine in different cancer cell lines [20]. The medications have different impacts on various subpopulations due to epigenetic modifications. This might help in guiding future clinical applications of these treatments [21].

Histone deacetylase inhibitors (HDACIs) are another family of epigenetic modifiers that are therapeutically employed in the clinical practice [22–24]. HDAC enzymes may modify chromatin topologies and facilitate cancer-related gene silencing in cancer cells, among other roles, as components of repressive protein complexes comprising DNMTs. As a result, inhibiting HDAC enzymes may result in the reversal of cancer's aberrant gene silencing. Several HDACIs have been demonstrated to have powerful anti-tumor properties and are now being tested in clinical studies. The FDA has authorized two such inhibitors, romidepsin (aka depsipeptide or FK228) and vorinostat (aka suberoylanilide hydroxamic acid or SAHA), for the treatment of cutaneous T-cell lymphoma [10,23,24]. Apart from antitumor activity, other possible applications of HDACIs and other epigenetic modifiers in clinical oncology are being investigated. According to Sharma et al. [25], drug resistance may be mediated by epigenetic processes and may be reversed with the use of certain HDACIs. This indicates a potential use of epigenetic treatment to overcome resistance, and to increase tolerance or potentiate the effects of traditional chemotherapy in the clinical treatment of cancer, where drug resistance has traditionally been a major issue.

Given that DNA methylation-mediated aberrant gene silencing in cancer requires transcriptional repressive complexes comprising both DNMTs and HDAC, targeting both enzymes with a DNMT inhibitor and an HDAC inhibitor in combination treatment is an appealing cancer management strategy. Indeed, using an HDAC inhibitor after a DNA demethylating drug has demonstrated to have synergistic benefits in in vitro gene re-expression as well as improved anti-tumor effects in clinical trials [26,27]. Moreover, epigenetic-modifying medicines may work in tandem with other traditional chemotherapeutic treatments to

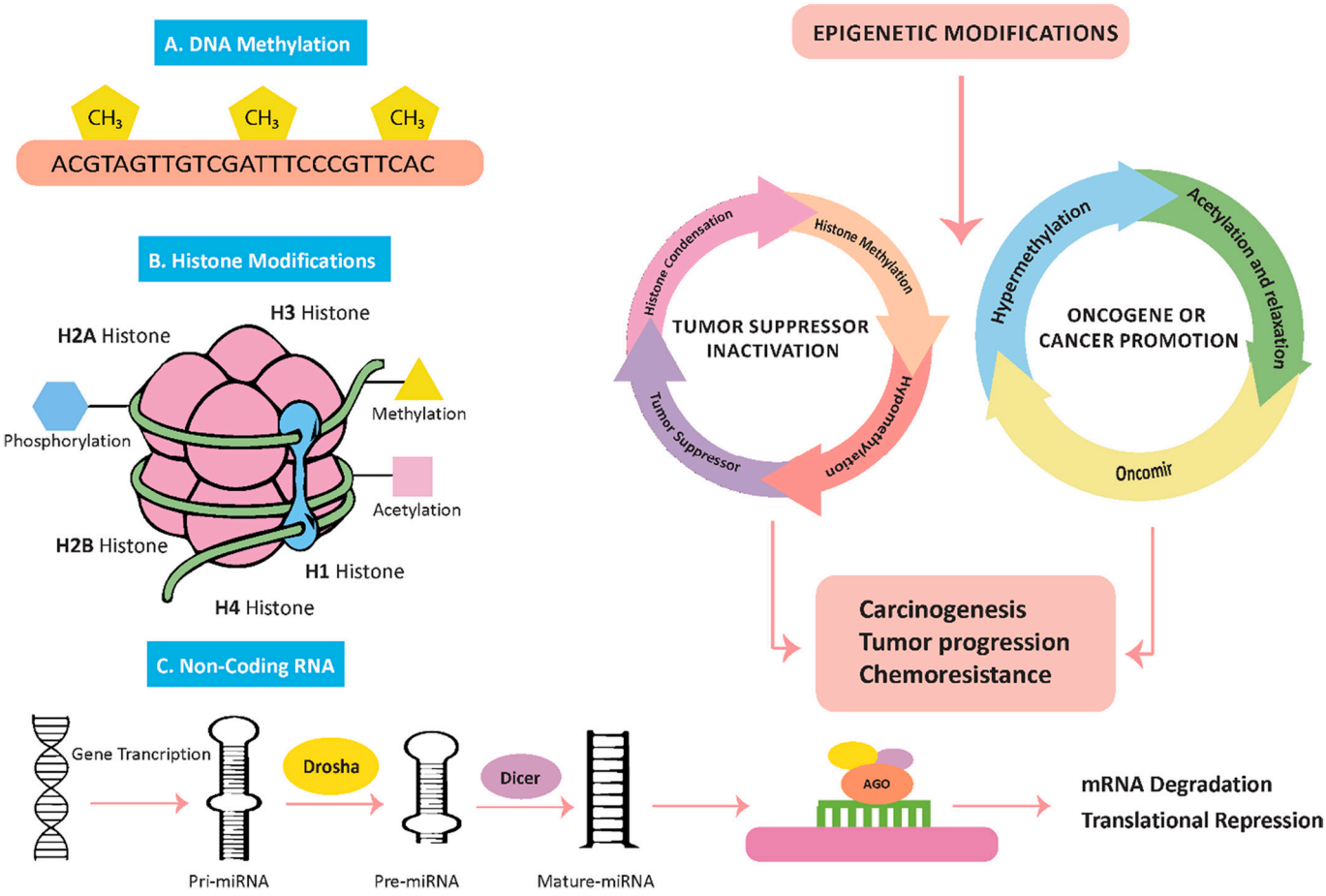

Fig. 1. Epigenetic modifications include A. DNA methylation; B; histone modification and C: Non-coding RNA. These events lead to carcinogenesis, tumor progression and chemoresistance followed by promotion of oncogenes and inactivation of tumor suppressors. Cancer promotion events include hyper methylation, oncomir, acetylation and relaxation while tumor suppressor inactivation includes Histone condensation, histone methylation, hypomethylation and tumor suppressor.

increase clinical effectiveness with lower dosages of either therapy. For instance, decitabine and azacitidine may alter various cellular pathways via gene reactivation, making cancer cells more susceptible to other treatments that target comparable pathways.

Both azacitidine and decitabine, while showing the clinical efficacy in haematological malignancies at low doses (when administered alone or in combination with other drugs), exert comparable anti-cancer activities in solid tumors (when administered at similar dosing schedules) remains a matter of investigation. For example, patients with metastatic lung cancer who have failed multiple lines of previous chemotherapy have achieved a robust and durable response in a clinical trial using a low-dose regimen of azacitidine and an HDAC inhibitor, entinostat (also known as SNDX-275 or MS-275) [10,27–30]. Clinical trials are currently being conducted for a variety of tumor types, including breast and colon cancer. In addition to clinical efficacy, extensive research is required in the context of clinical trials to optimize patient benefits, such as optimizing dose schedules and sequences and to identify individuals who could benefit from epigenetic treatment. Combining epigenetic and immune-based therapies to reduce cancer resistance.

2. Combining epigenetic and immune-based therapies to reduce cancer resistance

The integration of epigenetic medicines with other treatments, including standard chemotherapy, targeted therapies, and immunotherapy, has evolved as an attractive alternative for cancer treatment (shown in Fig. 2). Rational combination regimens offer the ability to overcome the limitations of single agent epigenetic treatments, thereby boosting antitumoral effects and decreasing drug resistance. Several studies are now being conducted to assess the effectiveness of various drug combination medicines, several of which have reached the clinical trial stage [31].

2.1. Synergies in epigenetics

Given the complexities of epigenetics regulation during carcinogenesis, the administration of a “cocktail” of epigenetically-targeted drugs could constitute a logical and viable therapeutic strategy [34]. Closed chromatin states characterised by underacetylated histone lysines are frequently associated to heavily methylated DNA sequences [35]. Therefore, low dosages of DNA demethylating agent accompanied by HDAC inhibition was shown to foster the reactivation of cancer-silenced genes [36]; contextually, preclinical studies revealed that coupling HDAC and DNMT inhibitors has a synergistic impact on tumor-suppressor gene reactivation, apoptosis induction, and cell division/growth inhibition in cancer cells [37]. Regimens based on combinations of DNMT and HDAC inhibitors have demonstrated early effectiveness and are being studied extensively in solid and haematological malignancies as shown in Table 1. Combined vorinostat/decitabine treatments, for example, showed therapeutic advantages in paediatric patients with secondary MDS/acute myeloid leukemia (AML) associated with solid tumor recurrence, including disease stability and a good

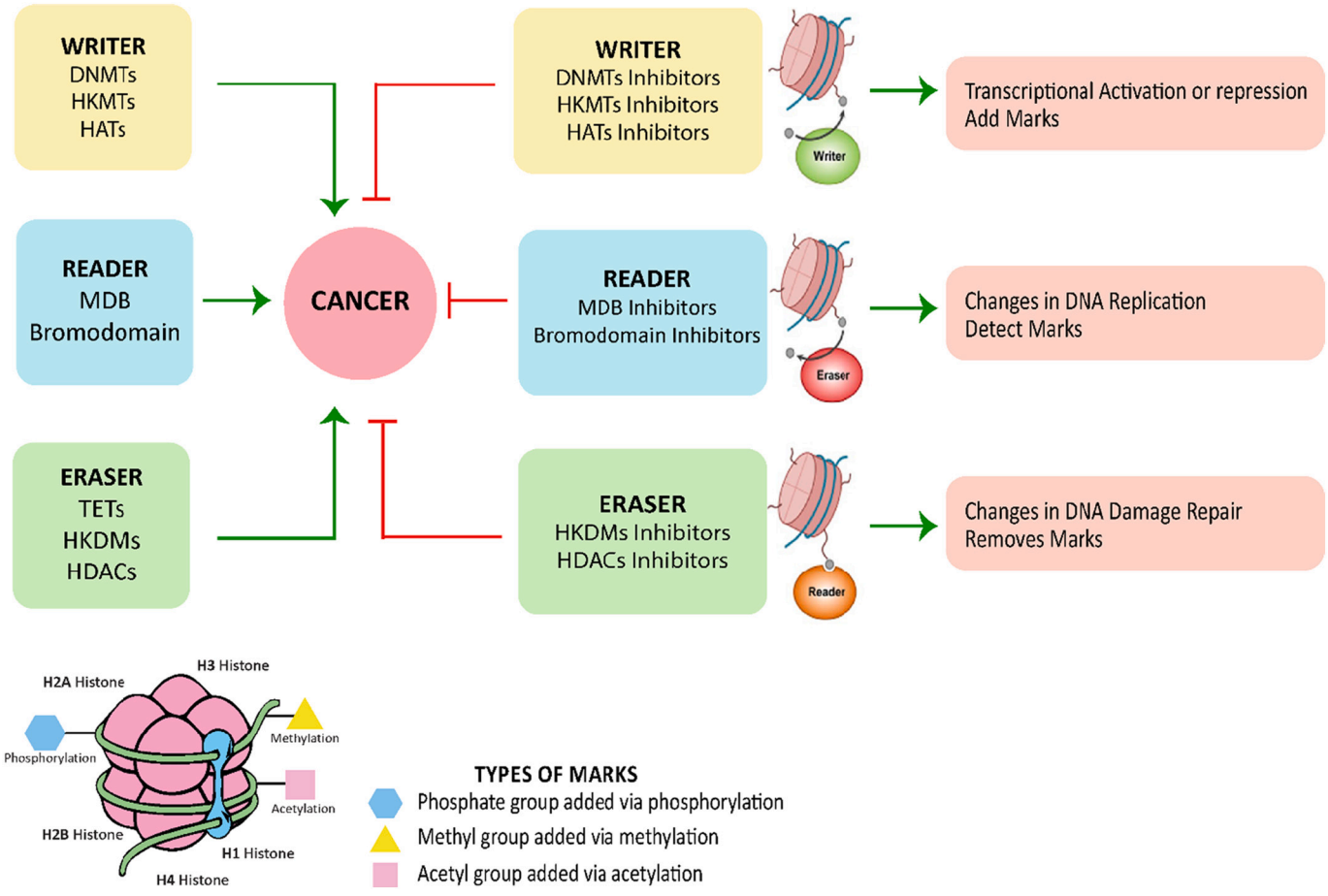

Fig. 2. Combining epigenetic drugs with other therapies for the treatment of cancer. When epigenetic drugs are combined with chemotherapy, they reverse chemoresistance associated epigenetic programming. Epigenetic drugs with targeted therapy prevent kinase reprogramming, overcome BCL-2 resistance and reverse endocrine resistance. When epigenetic drugs are combined with immunotherapy, they upregulate dsRNA which leads to accumulation of antigen presenting cells that promotes IFN signalling and activates MHC class I molecules and T-cells, ultimately inhibiting chemorestistance. Tumor antigens, and PD-1 ligands, activate ERVs, and IFN expression along with stimulation of anti-tumor immunity [32,33].

Table 1
Clinical status of combined therapy of HDACi and DNMTi.

NCT number	Drug	Combination therapy	Cancer type	Phase	Status
DNMTi					
NCT03913455	Guadecitabine	Carboplatin	Small cell lung cancer, extensive-stage small cell lung cancer	II	Active, not
NCT03308396		Durvalumab	Advanced kidney cancer, kidney cancer, clear cell renal cell carcinoma	IB/II	recruiting
NCT03576963		Nivolumab	Colorectal adenocarcinoma, CpG island methylator phenotype, metastatic microsatellite stable colorectal carcinoma	IB/II	Withdrawn
NCT03264404	Azacitidine	Pembrolizumab	Pancreas cancer	II	Active, not
NCT03019003		Durvalumab, Tremelimumab	Head and neck cancer	IB/II	recruiting
NCT04490707		Lenalidomide	Acute myeloid leukemia in remission	III	Recruiting
NCT03094637		Pembrolizumab	High risk myelodysplastic syndrome, IPSS risk category intermediate-1, myelodysplastic syndrome	II	Active, not recruiting
NCT03295552	Decitabine	Carboplatin	Metastatic triple negative breast cancer	II	Terminated
NCT02957968		Pembrolizumab followed by standard neoadjuvant chemotherapy	Breast adenocarcinoma; estrogen receptor-negative breast cancer; estrogen receptor-positive breast cancer	II	Active, not recruiting
NCT03709550		Enzalutamide	Castration-resistant prostate carcinoma, metastatic prostate carcinoma in the soft tissue	Ib/II	Withdrawn
NCT04353479		Camrelizumab (SHR-1210)	Acute myeloid leukemia	II	Not yet recruiting
NCT02159820		Carboplatin-Paclitaxel	Primary malignant neoplasm of ovary; FIGO stages II to IV	II/III	Recruiting
NCT04510610		Camrelizumab	Hodgkin lymphoma	II/III	
NCT04049344		Oxaliplatin	Metastatic renal cell carcinoma	II	Unknown
HDACi					
NCT04651127	Chidamide	Toripalimab	Cervical cancer	Ib/II	Recruiting
NCT04562311		Tislelizumab	Bladder cancer stage IV	II	
NCT03742245	Vorinostat	Olaparib	Relapsed/refractory and/or metastatic breast cancer	I	
NCT03848754	Pracinostat	Gemtuzumab Ozogamicin	Relapsed adult AML		Completed
NCT03829930	Entinostat	Enzalutamide	Prostate adenocarcinoma		Terminated
NCT03939182	Abexinostat	Ibrutinib	Diffuse large B-cell lymphoma and mantle cell lymphoma	I/II	Active, not recruiting
NCT02616965	Romidepsin	Brentuximab vedotin	Cutaneous T-cell lymphoma (CTCL)	I	Recruiting
NCT03024437	Entinostat	Atezolizumab and Bevacizumab	Metastatic cancer, renal cancer	I/II	Suspended
NCT03903458	Tinostamustine	Nivolumab	Malignant melanoma	I	Recruiting
NCT03820596	Chidamide	Sintilimab	Extranodal natural killer/T cell lymphoma	I/II	Completed

quality of life [38]. Another study reported that coupling entinostat (another HDACI also known as SNDX-275 and MS-275) with low-dosage azacitidine results in objective and long-term responses in individuals with resistant advanced non-small cell lung cancer (NSCLC) [39].

Pinometostat, a disruptor of telomeric silencing 1-like (DOT1L) inhibitor, has exhibited synergic effect with azacitidine in MLL-rearranged leukemia cells [40]. A clinical trial evaluating the efficacy, tolerance, and initial anticancer efficacy of pinometostat in conjunction with azacitidine for the management of patients with mixed linage leukemia (MLL)-rearranged AML is now active. Furthermore, the bromodomain and extraterminal (BET) inhibitor JQ1 in conjunction with azacitidine has been shown to synergistically cause apoptosis in AML and MDS, indicating that inhibiting both BET proteins and DNA methylation at the same time is a promising therapeutic route [41]. Contextually, a phase 1 trial in patients with non-Hodgkin lymphoma (NHL), MDS or AML was recently concluded aiming at examining the feasibility, pharmacologic, and anticancer effects of a new BET inhibitor, FT-1101, either alone or in conjunction with azacitidine approved by clinicaltrials.gov (NCT02543879).

2.2. Combination with chemotherapy

Coupling epigenetic agents with chemotherapeutic drugs that cause DNA damage has emerged as an appealing strategy for preventing or defeating resistance phenomena [42–44]. Chemoresistance is typically coupled with epigenetic programming, such as aberrant methylation of DNA and alterations in histone acetylation, which can be restored by DNMT and HDAC inhibitors [45–47]. This aberrant DNA is associated with methylation of key genes in mTOR signalling/AKT/PTEN/PI3K pathway which promotes resistance in various solid tumors via alteration in cell survival, motility, apoptosis, angiogenesis, cell metabolism and cell proliferation [48]. As an example, the low-dose DNMT inhibitor decitabine has been demonstrated to re-sensitise chemotherapy resistant diffuse large B cell lymphoma (DLBCL) cells to doxorubicin without causing significant damage [49]. Based on preliminary findings, a phase 1 clinical study in DLBCL patients evaluating azacitidine priming preceded by conventional chemo-immunotherapy R-CHOP (a drug cocktail including the monoclonal antibody rituximab, cyclophosphamide doxorubicin hydrochloride, vincristine and prednisolone) revealed that the combined treatment is well absorbed and resulted in a high rate of full remission [50]. HDAC inhibitors, like DNMT inhibitors, have been shown to alleviate resistance against chemotherapy, reprogramming cancer cells to respond to cytotoxic treatments [51,52]. Panobinostat, for example, inhibits resistance against cisplatin induced by hypoxia in NSCLC cells by destabilising HIF-1α [51]. HIF-1α activation causes resistance against various other chemotherapeutic agents like 5-Fluorouracil, Actinomycin D, Bleomycin, Carboplatin, Cisplatin, Docetaxel, Doxorubicin, Etoposide, Gemcitabine, Irinotecan, Melphalan, Methotrexate, Oxaliplatin, Procarbazine and Sorafenib [53].

2.3. Coupling with targeted treatment

The development of targeted treatments, which utilize chemicals intended to specifically interact with certain mutant/aberrantly signalling proteins, has constituted a real shift in cancer therapy paradigm [54]. Pharmacological treatment of mutant kinases produces fast clinical outcomes in genetically specified populations [55–57]. Resistance against targeted therapy, on the other hand, is almost unavoidable [57–63]. Genetic changes and transcriptional reprogramming are two resistance mechanisms that can be reversed using epigenetic treatments [32,64–67]. Epigenetic alterations are involved in oncogenesis of NSCL but its role in EGFR-TKI resistance is still uncharacterized. However, HDAC inhibition was reported to overcome tolerance to a variety of kinase inhibitors. For example, a relatively novel oral histone

deacetylase inhibitor MPT0E028 was able to rise apoptosis induced by the first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib in EGFR-TKI resistant NSCLC cells [68]. Another preliminary research reported that combining EGFR-TKIs and vorinostat reversed EGFR-TKI resistance and promoted apoptosis in NSCLC cell models [69]. HDAC inhibitors have also been shown to reverse the mammalian target of rapamycin (mTOR) TKI resistance in a number of malignancies as it has been observed that methylation of genes impact mTOR signalling pathway due to epigenetic alteration [48,70,71]. Resistance to mTOR inhibitors is caused by increased levels of protein kinase B (aka AKT) phosphorylation, which can successfully be suppressed by inhibiting HDAC. Accordingly, for example: i) HDAC inhibitors such as apicidin, vorinostat and panobinostat for example were shown to synergize with specific mTOR inhibitors to combat apoptosis resistance in B-cell acute lymphoblastic leukemia (ALL) cells [71]; ii) a combination of valproic acid and the mTOR inhibitor temsirolimus inhibited cancer cell proliferation and causes autophagy-mediated cell death in Burkitt leukemia/lymphoma patients [70]; and iii) a phase 1 trial in patients with advanced renal cell carcinoma (RCC) reported that, when mTOR inhibitors vorinostat and ridaforolimus were used in combined regimen, they were well-absorbed and resulted in long-term disease stability, indicating that more research into the combination therapy is promising and need to be further pursued in the future [72].

For the management of hematologic malignancies, DNMT inhibitors have been studied in conjunction with venetoclax, a specific inhibitor of the antiapoptotic B-cell lymphoma 2 (BCL-2) protein. Though venetoclax monotherapy shows promise effectiveness in leukemia patients, resistance toward venetoclax has been documented to develop rapidly [73,74], with upregulation of two antiapoptotic proteins, induced myeloid leukemia cell differentiation protein (MCL-) and B-cell lymphoma-extra-large protein (BCL-XL), being involved in the resistance mechanism [74]. When coupled with a BCL-2 inhibitor, azacitidine has been shown to reduce BCL-2 inhibition resistance by decreasing the expression of MCL-1, hence synergistically increasing apoptosis [75]. Venetoclax in combination with azacitidine or decitabine had an acceptable safety record and an enhanced success rate in elderly AML patients when compared to azacitidine or decitabine alone [76]. The combination of DNMT inhibitors and venetoclax has been designated as a “break-through therapy” by the FDA for earlier non-treated AML patients who are ineligible for intense chemotherapy, and it is now being tested in clinical studies for the management of MDS and AML.

2.4. Coupling with immunotherapy

Immune checkpoint therapies, involved in boosting anticancer immune responses by preventing checkpoint molecule interaction, have resulted in a significant advancement in cancer treatment [77–79]. Even though immunoglobulins against checkpoint proteins such as CTLA-4 (aka cluster of differentiation 152 or CD152), programmed death-ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1 or CD279) exhibited promising anticancer effects, their therapeutic use may be restricted due to poor antigen presentation and inadequate T-cell response. These limitations can be overcome by immunomodulatory actions driven by epigenetic remodelling [33,80–84]. Inhibiting epigenetic regulators such as lysine-specific demethylase 1A (LSD1), enhancer of zeste homolog 2 (EZH2), HDAC and DNMT elicit several immunomodulatory actions in cancer cells, including overexpression of MHC class I molecules, tumor antigens, and PD-1 ligands [85]. Knocking out such epigenetic proteins also initialises the production of endogenous retroviral components and double-stranded RNA in cancer cells, that also activates interferon signalling, helps to stimulate antineoplastic T-cell immunity, and makes cancer cells more susceptible to checkpoint blockade therapies [86]. These findings support the use of epigenetic agents in conjunction with immunotherapies.

Recent efforts have shown that DNMT inhibitors can improve the preliminary effectiveness of immunotherapies in a variety of malignancies. For instance, decitabine promoted the infiltration and anticancer activity of cytolytic $CD8^+$ T lymphocytes in a syngeneic mouse ovarian cancer model, and combining decitabine and anti-CTLA-4 antibody displayed synergistic antitumor effects and longer mouse survival [87]. Further studies showed that DNMT inhibition caused overexpression of MHC class I proteins, T-cell chemotaxis, and tumor infiltration of $CD8^+$ T cells in animal studies of prostate, colon and breast malignancies, hence amplifying the anticancer effects of anti-PD-1 antibodies [88,89]. Finally, a phase 2 research involving AML patients found that the combination of azacitidine with the PD-1 antibody nivolumab was safe and offered encouraging objective response rates and overall survival results [90].

In animal models of different malignancies, HDAC inhibitors have been shown to be effective when used with immunotherapies. For example, the HDAC inhibitor panobinostat increases PD-L1 and PD-L2 expression in melanomas and improves anti-PD-1 antibody therapy, resulting in decreased tumor growth and enhanced survival when compared to single-agent therapies [91]. Furthermore, the HDAC inhibitor belinostat enhanced the anticancer effects of anti-CTLA-4 treatment in a murine model of hepatocellular carcinoma, with increased IFN-γ generated by antitumor T-cells and decreased regulatory T cells [92]. Interestingly, entinostat was reported to suppress regulatory T cells and to improve the anticancer effects of IL-2 and vaccination treatment in animal studies of prostate and renal cancer [93]. According to the first report of clinical studies coupling HDAC inhibitors and IL-2 immunotherapy, the combination treatment improved actual response rate and median progression-free life in patients with metastatic RCC [94]. Given the importance of epigenetic regulators in modifying antitumor immunity, T-cell fatigue, immune cell infiltration, and function, a significant number of current clinical trials are assessing the effectiveness of coupling epigenetic medicines with immunotherapies. Future research will describe the impact of epigenetic agents on tumor and immune cell populations, as well as give insight into the molecular processes behind epigenetic therapy responses, which will aid in the development of rational combination treatments.

3. Epigenetic tools

Both genome compaction and gene expression are regulated by epigenetic alterations operated by certain enzymes (referred to as *writers*) and identified by effector proteins (known as *readers*). The majority of, if not all, epigenetic marks are reversible, and they may be removed using a variety of other enzymes called *erasers*. They have shown promising results when they are used in combination with other chemo and immunotherapeutic agents [95]. The development of numerous small molecule medicines is presently focused mostly on these epigenetic regulatory factors. Even though the FDA has only approved a small number of epigenetic medications for the treatment of cancer, many good epigenetic medications have undergone clinical trials and have had outstanding outcomes [96]. There isn't much evidence, though, that epigenetic medications and cancer therapy work in conjunction [95]. The intricate interaction of these three protein groups regulates gene transcription, and abnormalities in this system may ultimately lead to tumor initiation and development (shown in Fig. 3).

3.1. Epigenetic writers

Epigenetic writers oversee promoting the addition of active and suppressive tags to DNA or histones. Among the plethora of chemical groups that can be added to DNA and histone proteins by a variety of writer enzymes [97], the two most common epigenetic alterations are methylation – that occurs on both histone proteins and DNA and acetylation, which occurs solely on histones [98]. These two changes commonly influence cellular gene expression patterns by switching between transcriptional activation and suppression [99]. Histone

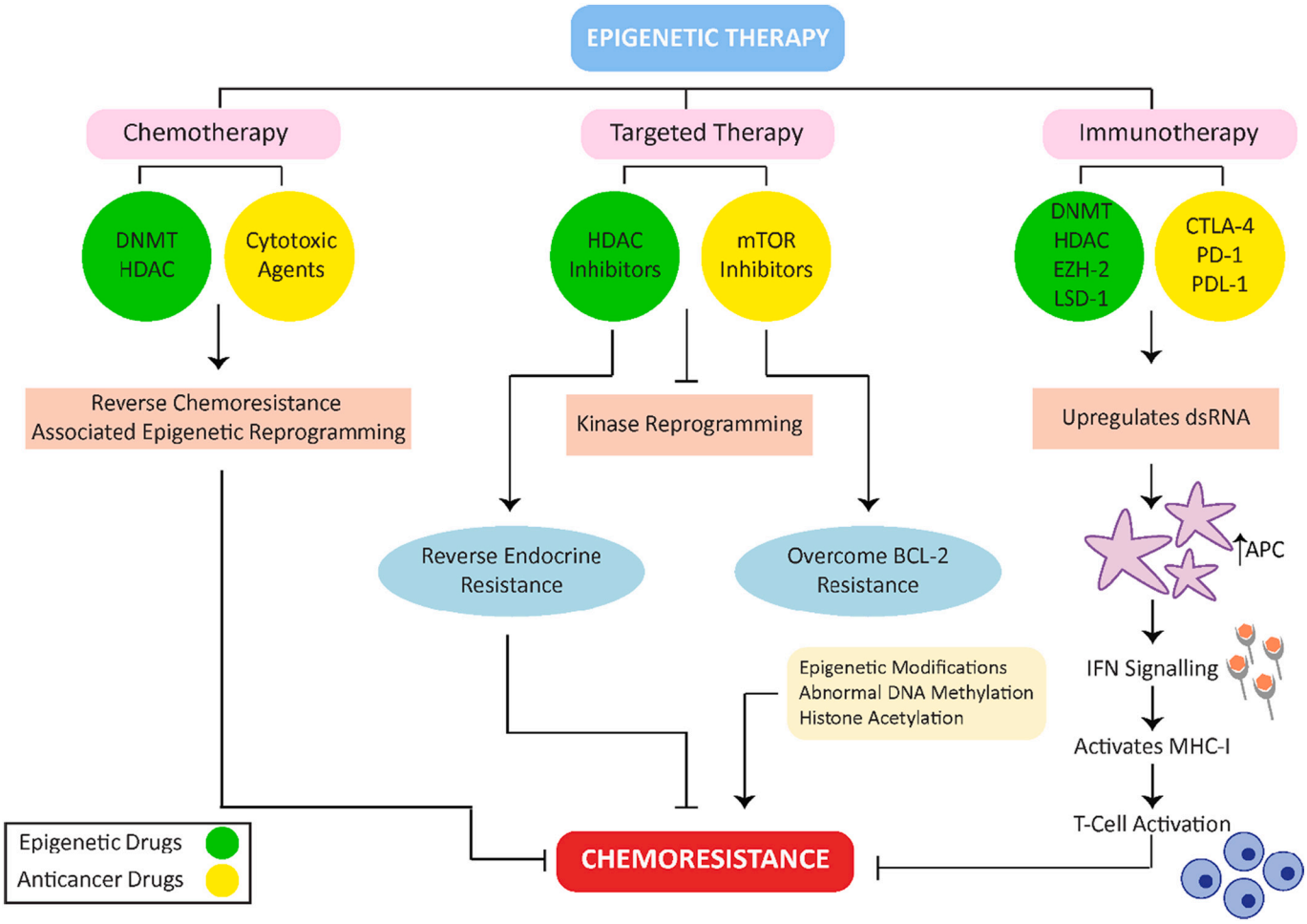

Fig. 3. Landscape of epigenetic marks, writers, readers and erasers. Inhibitors of epigenetic writers add marks, inhibitors of epigenetic readers detect marks and inhibitors of epigenetic erasers remove marks which leads to treatment of cancer. Writers cause various chemical modifications on histones and DNA; readers are proteins with special domains that interpret and identify those modification while erasers are group of enzymes which is proficient in removing chemical tags. Tumorigenesis is largely influenced by altered control of these epigenetic tools.

methyltransferases (HMTs, including histone lysine methyltransferases and protein arginine methyltransferases), histone acetyltransferases (HATs) and DNMTs are all remarkable examples of writer proteins [100], with DNMTs being the most attractive targets for therapeutic research, and clinical studies are underway for a number of inhibitors like azacytidine and decitabin to target these proteins [9,101].

3.2. Epigenetic readers

To moderate the impact of the variety of alterations performed by epigenetic writers, other cellular proteins must identify them and control their activity [102]. In mammalian cells, many protein domains that bind to these alterations have emerged, and these proteins are referred to as known as epigenome readers [103]. Numerous chromatin modifiers function as epigenetic readers owing to the existence of specialized domains capable of recognizing and binding various covalent changes to DNA and histones. Limiting again to the two most extensively studied histone modifications (methylation and acetylation), the methyl-CpG-binding domain (MBD) family of proteins are key DNA methylation readers because they attract chromatin remodellers, HDACs, and methylases to methylated DNA associated with gene regulation [104,105]. Interestingly, some MBD proteins may also bind unmethylated DNA through alternative regulatory domains or association with components of the Mi-2/nucleosome remodelling and deacetylase (NuRD) complex [106]. In addition, the Kaiso family proteins and the SET- and Ring finger-associated (SRA) domain family are also effective DNA methylation readers, while DNA methylation *editors* are a new group in this class of epigenetic modifiers (comprising the ten–eleven translocation (TET) protein family), which form 5-hydroxymethylcytosine (5-hmC) by converting the carbon-5 methyl group in 5-mC into an -OH group [107–109]. The category of methylated histone readers includes a wide range of proteins that have specific domains in charge of recognizing such modifications. So far, readers of methyl lysine and/or arginine residues have been located in, e.g., the royal superfamily domains (which include Tudor, tandem Tudor (TT), chromo and double chromo, malignant brain tumor (MBT), Pro-Trp-Trp-Pro (PWWP) and agenet domains), WD40 repeat (WDR) domains and plant homeodomains (PHDs), among others [110–112].

3.3. Epigenetic erasers

Post-translational changes on histones and covalent alterations on DNA are not persistent epigenetic markers [113] and, as such, they can be removed based on the cell's need to modulate the expression levels of the specific locus [114,115]. To the purpose, epigenetic erasers delete DNA or histone changes established by writers to control gene expression. Interestingly, eraser proteins like HDACs, histone demethylases (HDMs), LSD1 and ten-eleven translocation (TET) enzymes have all been linked to cancer, and many inhibitors of HDAC and LSD1 have made their way to clinical trials [101]. Because of the availability of specific

domains that can recognise and bind various covalent modifications found on DNA and histones, many chromatin modifiers operate as epigenetic erasers [116]. For the sake of brevity, in what follows only protein domains that can detect and bind to methylated DNA and those domains that can recognise and bind to the two commonly studied histone modifications, acetylation and methylation [98] will be discussed.

As discussed above, histone acetylation is an essential method in epigenetics for lowering chromatin condensation and so increasing gene transcription, but another significant process is the removal of acetyl groups through the activities of histone deacetylases (HDACs). HDACs are classified into two groups: group I and group II. Group I enzymes, which are further subdivided into classes I, II, and IV, comprise zinc-dependent amidohydrolases, while group II enzymes, also known as class III or sirtuins (SIRTs), rely on nicotinamide adenine dinucleotide (NAD) as a cofactor [117–119]. Interestingly, SIRTs play a role in transcription control, metabolic regulation, cell survival, and a variety of other biological processes and because numerous SIRT inhibitors have been found to have anticancer properties, some SIRTs like, e.g., SIRT1 to SIRT7 might be interesting therapeutic targets for cancer treatment [120]. Histone phosphatases may bind to histone proteins that have phosphorylated serine, threonine, or tyrosine residues, and several protein Ser/Thr phosphatases have been shown to dephosphorylate histone proteins, including PP1, PP2A, and PP4 [121–123]. Proteases known as deubiquitinating enzymes catalyse the removal of ubiquitin groups from histone lysine residues (DUBs) [124]. Additionally, they may be classified as ubiquitin-specific proteases (USPs) and Jab1/MPN domain-associated metalloisopeptidase (JAMM) domain proteins [125]. Both members of the USP and JAMM families have been demonstrated to target histone proteins H2A and H2B, which control transcription, DNA repair, gene expression, and cell cycle progression [126,127]. While histone ubiquitination activities are less well known than those of other histone modifications, mounting evidence suggests that this epigenetic change plays a critical role in the DNA damage response [128]. Lysine-specific demethylase 1 (LSD1 aka KDM1) is the first reported histone demethylase, and features an amino oxidase domain that interacts with flavin adenine dinucleotide (FAD) as a cofactor required for demethylation [129]. Since then, a new class of lysine demethylases known as Jumonji C domain-containing demethylases has been discovered (JMJD), that require Fe^{2+}/2-oxoglutarate (2-OG) in place of FAD for activity [130]. Interestingly, within JMJD proteins, there is currently just one enzyme, JMJD6, with is endowed with arginine demethylase activity [131].

4. Old drugs repurposed as novel epigenetic inhibitors

The conventional drug development process is expensive and time-consuming; moreover, the actual success rate of a drug candidate reported in the last decades ranges from 10 % to 20 %. With these limitations in mind, alternative approaches have been investigated, and the drug repurposing approach has evolved as an intriguing possibility in the treatment of numerous illnesses [132–134]. Different drug repurposing (DR) methods may be adopted to find possible repurposing medications, including network-based procedures such as semantic-based methods, clustering, text mining-based and propagation [135]. DR is a significant tool for developing innovative, tailored therapeutics; accordingly, the next paragraphs will be dedicated to a brief survey of various drugs that have been repurposed for epigenetic targeting, including BET, HDM, HAT, DNMT, HMT inhibitors and histone modulators alone or in combination [136–140].

The strategy of repurposing old drugs – for which crucial information like safety and pharmacokinetic characteristics are already known – for epigenetic-targeting might sidestep the traditional paradigm, in which the primary goal is to create one-indication-only drugs, since epigenetic pathways are common across various cancer models. Contextually, it can provide patients with lower-cost treatments and a revolutionary precision medical approach to maximize therapeutic effectiveness and minimize toxicity, as shown in Table 2. Apicidin, Mahanine, Berberine, DNMTi HDACi TSA, Procainamide and Hydralazine are just a few examples of successful epidrug repurposing [141]. These chemicals have been reported to be efficient in many tumor models, and hence appear to be endowed with promising potential for further research and development [142]. Interestingly, however, although many tumor models have similar interactions between repurposed medicines and epigenetic enzymes, the results of epigenetic repression may vary. Depending on the tumor model, abnormal epigenetic pathways generate unique modifications in cell cycle, expression of genes and proliferation, which may have a differential influence on levels of gene expression [143].

The most investigated epigenetic targets are the HDAC and DNMT enzymes. As mentioned earlier, changes in expression of DNMT and HDAC are connected in cancer, causing tumor suppressor gene expression to be downregulated [144]. As a result, active compounds that target both HDAC and DNMT enzymes might be a more effective solution with respect to single target agents [145]. BET, HMT, HAT and HDM inhibitors have piqued the scientific community's interest in recent years, with various drugs showing potential as repurposed blockers of these histone modulators [146,147]. As a partial drawback, HDAC enzymes are ubiquitously expressed, and because of the variety within subclasses, it is difficult to design novel treatments targeting these epigenetic enzymes [148]. Nonetheless, a number of licenced medications have being investigated as effective HDACi [149,150]. Contextually, DNMT inhibitors (DNMTi) are also widely studied, and several medications have been successfully repurposed as DNMTi [151,152].

5. Epigenetic editing

Epigenetic editing is the use of epigenetic enzymes to rebuild the localized epigenetic environment of an internal genomic region, usually with the goal of regulating transcription. The use of sporadically interspaced small palindromic repeats d-Cas9 has considerably enhanced epigenetic editing progress, resulting in preclinical pharmacological achievements with a range of epigenetic enzymes [188–190]. Epigenetic modification tools - such as DNA binding proteins like transcription activator-like effector nucleases (TALENs) or zinc finger nucleases (ZFN), which are linked to epigenetic modifiers - were found to be capable of introducing epigenetic alterations to a specified locus [191,192]. TAL effector repeats, which display a modular architecture that includes a central DNA-binding region comprising a tandem array of nearly identical repeats that are almost all 34 residues long - are the DNA-binding structures that may be engineered to interact with almost any genomic sequence [193,194]. Maeder et al., for instance, discovered that fusing modified TALE repeated arrays with the TET1 hydroxylase catalytic site allows effective and selective demethylation of particular CpGs in living cells [195]. The authors showed that these TALE-TET1 combinations allow the alteration of crucial methylated promoters CpGs, resulting in significant improvements in gene expression. Also, Mendenhall et al. showed that TALE effector can be coupled to LSD1 to effectively demethylate enhancers and disclose enhancer target genes [196]. According to their results, enhancer-associated chromatin alterations could be effectively removed from targeted loci by the fusion proteins, with little effect on controlled areas.

Recent advances in epigenome editing based on clustered regularly interspaced palindromic repeats (CRISPR)/Cas-based technologies have endowed researchers with powerful tools to site-specifically program epigenetic modifications to endogenous DNA and histones and to control native chromatin architecture. As a result, these systems have substantially contributed to uncover the intricacy of epigenetic events and give new insights into the role of chromatin abnormality in the insurgence of genetic disorders, as well as novel techniques for preventing or reversing this dysregulation [197,198]. The CRISPR/Cas9 epigenetic editing approach relies on an endonuclease protein whose DNA-targeting specificity and cutting activity can be programmed by a

Table 2
Repurposed drugs to target epigenetics.

Drug	Approved for	Epigenetic target	Cancer model	References
a) Candidates for non-cancer drug repurposing for inhibition of DNMT				
Procaine	Anesthesia via infiltration, peripheral nerve block, and spinal blockage	DNMT3A, DNMT1	NSCLC, gastric cancer, hepatocellular carcinoma, breast cancer	[139]
Procainamide	Cardiac arrhythmias	DNMT1	Prostate cancer	[153]
Mithramycin A	Hypercalcemia, particularly as a result of malignancy		Lung cancer	[154]
Laccaic acid A	Natural compound (NA)		Breast cancer	[155,156]
Harmine			Acute myeloid leukemia	[157]
Chlorogenic acid			Breast cancer	[158]
Hydralazine	Hypertension		T-cell leukemia, prostate cancer, cervical cancer, bladder cancer, breast cancer	[159–163]
Mahanine	Natural compound (NA)	DNMT3B, DNMT1	Prostate cancer	[164,165]
Nanaomycin A	Antibiotic quinone	DNMT3B	Burkitt lymphoma, colon cancer, lung cancer, T-cell acute lymphoblastic leukemia	[166,167]
Olsalazine	Ulcerative colitis, inflammatory bowel disease	DNMT	Cervical cancer	[168]
b) Candidates for non-cancer therapeutic repurposing for HDAC inhibition				
TSA	Antifungal antibiotic	SIRT6, HDAC class I, II	Prostate cancer, pancreatic cancer, leukemia, hepatocellular carcinoma, esophageal squamous carcinoma, colon cancer, breast cancer	[139]
Sodium butyrate	Anti-inflammatory	HDAC1	Breast cancer, gastric cancer, prostate cancer	[169]
Psammaplin A		SIRT1, HDAC6, HDAC1	Breast cancer, cervical cancer, endometrial cancer, lung cancer	[139]
HC toxin	Natural compound (NA)	HDAC	Neuroblastoma, breast cancer	[170]
Ginseng		HDAC	Non-small cell lung cancer	[171]
Aspigenin		HDAC class I	Prostate cancer	[172]
Carbamazepine	Seizures with psychomotor or focal characteristics can be controlled	HDAC7, HDAC6, HDAC3	Colon cancer, liver cancer, breast cancer	[139]
Artemisin	Malaria	HDAC6, HDAC1, HDAC2	Breast cancer	[173]
Apicidin	Antiprotozoal (NA)	HDAC8, HDAC3, HDAC4	Pancreatic cancer, ovarian cancer, oral squamous cell carcinoma, lung cancer, endometrial cancer, cervical cancer, colon cancer, breast cancer, acute promyelocytics leukemia	[139]
c) Candidates for non-cancer medication repurposing for BET, HMT, HAT and HDM inhibition				
Tranylcypromine	Phobic and panic disorders, dysthymic disorder, depression, atypical depression	LSD1	Sarcomas, glioblastoma multiforme	[174,175]
Pargyline	Antihypertensive, irreversible selective MAO-B		Prostate cancer	[176]
Geranylgeranoic acid	Natural compound (NA)		Neuroblastoma	[177]
Clorgyline	MAO inhibitor		Leukemia, colon cancer, bladder cancer	[178]
Garcinol	Antioxidant (NA)	KAT2B, Ep300	Cervical cancer	[139]
Nitroxoline	Urinary antibacterial agent	BRD4	Mixed-lineage leukemia	[179]
Plumbagin	Natural compound (NA)	KAT3B/p300	Liver carcinoma	[176]
Ribavirin	Hepatitis C, RSV infections	EZH2	Solid tumors	[180]
Anarcadic acid	Radio-sensitization activities, anti-inflammatory	Tip60, Ep300	T-cell lymphoma, prostate cancer, myeloid leukemia, lung cancer, cervical cancer	[181,182]
d) Candidates for non-cancer medication repurposing that inhibit both DNMT and HDAC				
Resveratrol	Natural compound (NA)	DNMT	NSCLC, breast cancer	[183,184]
Parthenolide	Anti-inflammatory (NA)	HDAC1	Myeloma, leukemia, breast cancer	[185–187]
Berberine	Fungal and parasitic infections	DNMT3A, DNMT1, HDAC class I, II, IV	Lung cancer, multiple myeloma, prostate cancer	[139]

short guide RNA (gRNA) [199,200]. In concomitance, nuclease-null disabled (or dead) CRISPR/Cas systems (dCas) coupled with effectors have transformed our capacity to edit the epigenome and have substantially advanced our knowledge of epigenetic control due to the relatively straightforward targeting of genomic DNA by modifying the protospacer sequence inside gRNAs. The gRNA targets particular loci and the effector can either activate or suppress transcription of genes, as shown in Fig. 4. The effectors are generated from epigenetic erasers and writers like TETs, HDAC, HMTs, HATs, HDM and DNMTs [201]. The Krüppel associated box enzyme linked to dCas9 is another potent epigenetic editing tool that may be employed for silencing of gene [202]. It has been demonstrated that dCas9-KRAB-mediated suppression is precise in blocking the activation of particular enhancers through epigenome alteration at the local level [203]. As a result, epigenetic editing might be viewed as a viable strategy for targeted gene therapy that can fix disease-related epi-mutations. It also acts as a valuable approach for identifying basic epigenetic concerns, such as the source and effect of epigenetic changes in expression of gene. Nonetheless, the most difficult issues facing epigenome editing are attaining non-immunogenicity, effective delivery and high sensitivity [188].

6. Epigenetics modulations by dietary compounds

Polyphenols produced from *Hibiscus sabdariffa* have been shown to alter expression of miRNA in hyperlipidemic mouse lacking the LDL receptors. These epigenetic alterations are becoming well recognised as important epigenetic gene regulatory mechanisms. Individual phenotypic heterogeneity is demonstrated accompanying cellular epigenetic

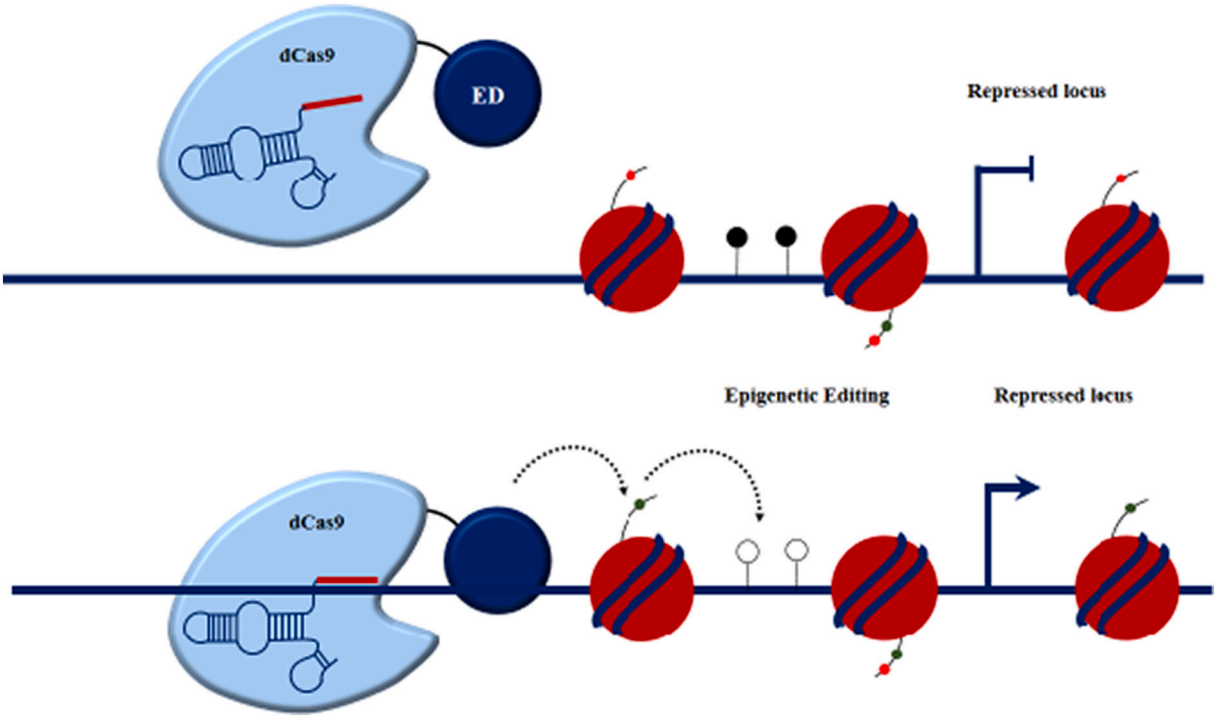

Fig. 4. Epigenetic editing with CRISPR/dCas9 through attachment on Effector domain (ED).

mosaicism even in genetically similar people. Nutritional and environmental variables have the capacity to impact organisms from infancy through adulthood, and transgenerationally via epigenetic changes affecting regulation of genes. Organisms have tissue-specific modification of histone and DNA methylation patterns. Plant-derived polyphenols such as catechins and curcumin are constantly in contact with enzymes along with epigenetic modulators such as miRNA, kinases, histone acetyltransferases, deacetylases along with DNA methyltransferases.

Fatty acids (FAs) have been linked to epigenetic processes that control expression of gene. Fatty acids have the ability to change the epigenomics and influence genes involved in the reduction of diabetes and insulin resistance (IR), along with improvement in metabolism of glucose and lipid. The capability of reprogramming epigenetic characteristics is intriguing for the treatment of chronic diseases. This is possible through changing one's lifestyles and consuming substances linked to epigenetic changes. Vitamins, polyphenols, phytochemicals, minerals, fatty acids, methyl donors and amino acids have all been identified as potentially harmful nutrients.

DNA methylation has been demonstrated to be influenced by polyunsaturated fatty acids (PUFAs), that is naturally occurring fatty acids featuring 2 or more double bounds along their hydrocarbon chain. Omega-3 (ω-3) polyunsaturated fatty acids (PUFAs) include α-linolenic acid (ALA; 18:3 ω-3), stearidonic acid (SDA; 18:4 ω-3), eicosapentaenoic acid (EPA; 20:5 ω-3), docosapentaenoic acid (DPA; 22:5 ω-3), and docosahexaenoic acid (DHA; 22:6 ω-3). These ω-3 PUFAs can be found both in plant and animal sources and are characterised by the presence of the first double bond located on the third carbon atom away from distal -CH_3 group. Omega-6 (ω-6) PUFAs, with the first double bond 6C atoms way from the terminal methyl group, are also present in both plant and animal diets, with linoleic acid (LA; 18:2 ω-6) and arachidonic acid (AA; 20:4 ω-6) being prime examples of these compounds. PUFAs are thought to be crucial mediators for promoting and sustaining human health throughout life. In particular, ω-3 PUFAs have recently been found to be advantageous in a variety of human pathologies, including obesity and diabetes mellitus type 2 (T2D), as well as being linked to a lower risk of stroke and atherosclerosis and, more generally, a lower risk of cardiovascular diseases.

Concerning their involvement in DNA modification, the Dietary ω-3 supplementation was explored for its epigenetic anti-obesity benefits in a 6-month supplementation trial on overweight and obese individuals, both as a preventative and therapeutic measure. This analysis was concluded by finding that 308 CpG sites comprising 231 genes had a changed methylation profile, with 286 hypermethylated and 22 hypomethylated patterns. These epigenetic changes were found to be significant for pathways involved in lipid metabolism, as well as a variety of other diseases. In a similar study, an energy-restricted diet combined with ω3-rich fish oil resulted in higher methylation levels of fatty acid desaturase 1 (FADS1, that encodes for the Δ-5 desaturase enzymatic step in the long chain PUFA biosynthetic pathway) and pyruvate dehydrogenase kinase 4 (PDK4, a kinase that plays a key role in regulation of glucose and fatty acid metabolism and homeostasis) at several CpG sites, as well as weight reduction. This latter beneficial impact was similarly linked to a change in the methylation status of CD36, a gene that encodes a multifunctional transmembrane glycoprotein required for metabolism of lipids. As a result, it may be implicated in obesity-related problems such as glucose intolerance and T2D.

An interesting study was focused on the impact of ω-3 on Yup'ik Eskimos in Alaska, who on average consume 20 times more ω-3 fats from fish with respect to all other USA residents. The result from this investigation suggests that a high intake of these fats contributes in preventing obesity-related chronic diseases such as diabetes and heart disease. The authors discovered 27 differentially methylated CpG sites in physiologically significant areas with epigenome-wide significance. Two meaningful correlations of PUFA consumption were found on chromosomes 3 (helicase-like transcription factor), 10 (actin 2 smooth muscle/FAS cell surface death receptor), and 16 (protease serine 36/C16 open reading frame 67), with 27 differently methylated CpG sites expected to reduce FAS expression. An apoptotic mechanism was supposed to govern and regulate lipid metabolism. Furthermore, ω3-FA ingestion influenced the methylation profile of the aryl-hydrocarbon receptor repressor (AHRR) gene. This impact was complemented by additional beneficial outcomes, such as increased glucose tolerance and insulin sensitivity. In another research, Mediterranean diet supplemented either

with extra virgin olive oil or nuts resulted in hypomethylation and improved the gene expression implicated in inflammatory and diabetic pathways. An examination of the impact of ω-6 consumption in women indicated a positive connection with waist circumference, truncal fat and body mass index (BMI), and linked high resulting of ω-6 intake to the hypermethylation of the tumor necrosis factor alpha (TNF-α) promoter.

In cultured human THP-1 monocytes (a cell line derived from an acute monocytic leukemia patient), the monounsaturated fatty acid (MUFA) oleic acid generated notable hypomethylation and an increased expression pattern when compared to arachidonic acid. Moreover, the inflammatory profile was improved because of this. Both MUFA and PUFA epigenetic effects are heavily influenced by subtype and dosage. Oleic acid, which is derived mostly from vegetables, is particularly beneficial epigenetically in factors linked to T2D, obesity and atherosclerosis.

A clear FA-induced memory was shown in an insulin-resistant (IR)-cellular model treated with high dosages of palmitate and in male Sprague-Dawley rats fed with a high-fat diet (HFD). This might be linked to changes in histone methylation levels, which have a stimulating impact, specifically on the forkhead box protein O1 (FOXO1) promoter. Palmitate promoted IR, which resulted in prolonged hyperglycemia and gluconeogenesis, indicating a type of cellular metabolic memory.

The implications of palmitate on genome-wide expression of mRNA and methylation of DNA in human pancreatic islet cells were examined by two different groups. Data were represented as DNA methylation alterations in various locations. The methylation of DNA was found to be altered in 290 genes, 73 of which were linked to BMI. Palmitate influenced the expression of 1860 genes related to gluconeogenesis, FA metabolism, T2D and glycolysis.

Maples and coworkers reported an increase in methylation affecting expression of peroxisome proliferator-activated receptor-delta (PPAR-δ) in human skeletal muscle cells in both severely obese and lean women in experiments utilising 1–1 oleate-palmitate combinations. The authors found that the previously indicated elevation in methylation of the same gene was less significant in obese women, suggesting that the degree of obesity affects methylation epigenetic modifications in an environment-specific approach. Another study showed that, in murine macrophages, stearate and palmitate boosted interleukin-4 (IL-4) levels along with PPARγ methylation, and such hypermethylation was thought to impact the proinflammatory implications of these saturated FAs, which has been linked to IR in obesity. The detrimental effects of certain saturated FAs on proinflammatory and metabolic abnormalities were studied further, with IR, hyperglycaemia, deregulation of lipid metabolism, lipotoxicity, T2D, fat build-up and obesity all being phenotypes apparently linked to epigenetic changes in methylation of DNA and acetylation of histone.

Short-chain fatty acids have less than 6 carbon atoms, are generated by fermentation of microbes, and are digestible in the large intestine. They have the potential to modify epigenetic profiles and, as a result, the expression of genes involved in lipid metabolism, insulin sensitivity, glucose homeostasis and cancer. Sodium butyrate (NaB) is one of such short-chain FAs that has been shown to decrease activity of HDAC. Indeed, Through HDAC inhibition and histone acetylation, NaB treatments reduced plasma glucose, glycated haemoglobin (HbA1c), beta-cell apoptosis, and improved plasma insulin level and glucose homeostasis in diabetic animals compared to controls. By modulating the p38/ERK MAPK and apoptotic pathways, NaB therapy enhanced beta-cell proliferation, function, and glucose homeostasis in juvenile diabetic rats, as well as reducing beta-cell death.

The beneficial NaB antidiabetic effect was affirmed in comparison to boosting type-1 fiber ratio, improving muscular acylcarnitine profile along with improving insulin sensitivity in relation to protective anti-obesity and prolonged adiposity and body mass utilising a C57BL/6 J mouse model under a HFD [150]. However, in chickens body weight reacted favourably to NaB under the influence of epigenetic modifications such as histone hyperacetylation. In another report, NaB was found to cause hypomethylation of genes involved in apoptosis, signalling and cell cycle processes or hypermethylation of genes associated with processing of RNA and transportation of protein in Chinese hamster ovary (CHO) cells. Both hypo- and hypermethylation effects were seen for genes involved in protein production, RNA metabolism and differentiation. The altered gene areas were thought to represent regulatory sequences that are strongly connected to the above mentioned cellular events to butyrate. NaB supplementation increased histone hyperacetylation in bovine cells, which was supported by the suppression of HDAC, among other alterations of genes involved in energy consumption, death, differentiation and cell cycle and growth.

Several more investigations supported the effect of butyrate in raising histone acetylation in promoting chemokine/cytokine production, cell proliferation, NF-κB, differentiation and proinflammatory response. As a protective effect of butyrate, NaB can modify the activation of androgen receptors in prostate cancer cells through increased acetylation of H4 and H4, resulting in tumor growth inhibition. Butyrate has a similar protective role in human gastric cancer cells, which was established by generating histone and demethylation changes in the promoter area of secreted frizzled-related protein 1 and 2 (SFRP1/2). NaB was also thought to be able to promote apoptosis and activation of caspase by using these pathways.

From all evidences discussed above, butyrate is endowed a wide range of actions, from adiposity, glucose homeostasis, increased insulin sensitivity, to maintaining body weight and reduced plasma glucose along with less desirable consequences including build-up of fat and IR. More research is however required to differentiate the consequences of metabolic and chronic conditions and the underlying processes, including epigenetic ones, in a preventative and therapeutic approach.

Trans-fatty acids (tFAs) - that is unsaturated fatty acids with one or more double bonds in a trans configuration which can be found in foods obtained from ruminants and in industrially produced, partially hydrogenated vegetable oils - have been shown to link metabolic diseases via epigenetics. High-density lipoproteins (HDLs) are associated to cardioprotection and transport functional miRNAs in circulation, and a dedicated investigation found that human miRNAs, particularly those linked to HDLs, were changed as a result of commercial tFA consumption. Interestingly, although the authors reported no significant variation in HDL-carried miRNA concentration between diets, differences in plasmatic pool contribution between diets were seen for miR-124-3p, miR-375, miR-150-5p, and miR-31–5p, and these miRNAs were shown to be more abundant in lipid metabolism pathways. Changes in miRNA were linked to interaction of extracellular matrix receptor and metabolism of lipid. As a result, miRNAs were suggested to have a role in the control of metabolism of plasma lipid levels. The industrially modified FAs' epigenetic activity was discovered to be passed on to succeeding generations. Elaidic acid (EA) supplementation to pregnant or lactation C57BL/6 mice is one example. Both exhibited widespread methylation induction in 3-month-old offspring adipose tissues, which associated with build-up of adipose tissue and, as a result, weight growth. In a reverse dose-effect relationship, EA was demonstrated to promote methylation in human THP-1 monocytes. In conjunction with DNA methylation, the gene expression that drives adipogenic and proinflammatory patterns was changed. Accordingly, these results showed that EA influences expression of genes via epigenetic processes. EA targets components that might be regulated.

In the initial stages of tumor growth, many epigenetic modifications of cancer-related genes take place in cancer cells. Interestingly, these epigenetic chromatin alterations are hereditary and transient, making them intriguing targets for the production of novel medications that target the epigenome and could improve current cancer treatments [204–207]. Utilising innovative treatment medications and individualized options improves patient survival. Alternative remedies represented by organic phytochemical components have been incorporated into several of these treatments. According to some reports, eating a diet

high in fruits and vegetables can greatly lower the chance of developing cancer because these foods include phytochemicals that may control oncogene expression and tumor suppressor genes. Surprisingly, phytochemicals may influence the epigenome via altering the activity of HDACs and DNMTs [208,209]. Generally, kinase inhibitors, personalized antibodies, chemo and radiotherapy agents, immune system stimulants, and other drugs are used to treat cancer. The abnormal epigenetic modifications gained during cancer were specifically reversed by HDAC inhibitors and demethylating medications, which altered gene expressions [210]. According to recent findings, natural substances and dietary supplements may be able to restore the normal epigenetic markers that are changed during carcinogenesis. Curcumin, EGCG, resveratrol, quercetin and SFN are the phytochemicals most thoroughly investigated in relation to cancer. According to numerous studies, these natural substances block a number of cellular processes linked to cancer. Particularly, these drugs restored the expression of tumor suppressor genes and inhibited the production of oncogenes, which prevented the growth and spread of tumors by specifically targeting important signalling mediators [211]. The management of the epigenetic system, which included the control of HDACs and DNMTs activities as indicated in Table 1, is one way that these effects are partially regulated.

7. Natural cancer treatments that target epigenetic processes

Due to the reversibility of epigenetic markers, they may be changed by a range of external and internal events. Several natural compounds generated from diverse sources have been discovered to directly affect different components of the cell's epigenetic machinery [212]. Given that dietary factors have been demonstrated to affect epigenetic variation, it is reasonable to expect that investigating strategies for modifying epigenetic variation using natural products may be effective in preventing and treating diseases such as cancer. [213]. In certain malignancies, epigenetic-related pathways can be influenced by nutritional and non-nutritional contents of vegetables and fruits through of tumor suppressor reactivation, oncogene suppression, cell cycle modulation and apoptosis induction [214]. Several natural substances have been confirmed to have a substantial importance in the restoration of abnormal epigenetic modifications in cancer in recent years, and a few of the most significant are discussed below. Compounds such as curcumin, epigallocatechin gallate (EGCG), genistein, quercetin, resveratrol and sulforaphane are known to inhibit tumor development in many models of cancer and are now in various phases of clinical studies for their use toward different malignancies. Curcumin, for example, has been certified by the FDA to be used as a nutritional supplement; consequently, understanding the activities of these chemicals offers considerable promise in the fields of chemoprevention and treatment [215]. These chemicals have been shown to be effective at reverting altered genes and enhancing the efficiency of traditional cancer therapies against expansive and malignant tumors. Furthermore, they have a significant advantage as a strong chemotherapeutic drug since they change cancer cells in a multi-targeted manner via numerous routes and mechanisms, particularly epigenetic mechanisms. As a result, natural materials may serve as sources of therapeutically useful epidrugs.

8. Microbiota-induced epigenetic alterations in the host

Microbiota, as an essential symbiont of the human body, may cause epigenetic changes in the host. More precisely, human body can respond to environmental signals through epigenetic mechanisms, changes in histone or methylation of DNA [255]. Gut microbiota influence host epigenetics largely through synthesizing metabolites to sustain the body's dynamic equilibrium, such as forming SCFAs to change the host epigenome that impacts the body's health and disorders [256–259]. Gut microbiota can produce biological chemicals as raw materials, such as acetyl or methyl groups for modification of histone or methylation of DNA that can alter host epigenetic mechanisms in pathologic and physiologic ways [260]. Previous studies looked at DNA methylation and expression of genes in the mucosa of Toll-like receptor 2 (TLR2) knockout mice. Two immune-related genes, namely interferon induced protein with tetratricopeptide repeats 2 (IFIT2, encoding a protein responsible for interferon stimulation) and alanyl aminopeptidase N (ANPEP, encoding a small intestine enzyme that plays a role in the final digestion of peptides generated from hydrolysis of proteins by gastric and pancreatic proteases), were hypermethylated in the promoter area of this $TLR2^{-/-}$ mouse model [261].

Changes in the composition of mucosal microbes are linked to epigenomic and transcriptome changes. A substantial difference in abundance was seen between wild-type and TLR2/animals for several microbes, including member of the Firmicutes genus. These findings imply that changes in composition of mucosal microbes mediated by TLR2 deletion may result in changes in epigenetic regulation [262]. Biomolecules synthesized by metabolising the host's nutrition, such as vitamins, tryptophan, SCFAs, polyamines, polyphenols and catabolites can be used to connect the gut microbiota to host epigenetics [263]. However, the fundamental molecular mechanism driving this interaction has not been extensively understood. According to research, SCFAs, which are among the most essential mediators, are involved in this interaction process. Rapid increases or decreases in SCFAs caused by dietary food consumption or ecological factors might result in epigenetic alterations in the host. Butyrate, for example, may increase intestinal growth and keep homeostatic balance, which it does through a variety of signal transduction pathways [264–267]. Furthermore, the gut microbiota can influence the responses of host cells to stimulus by modifying host epigenetics, which controls expression of genes [268]. Table 3 shows how compounds derived from microbiota and gut microbiota can trigger typical epigenetic modifications to govern numerous physiological activities of the host. SCFAs generated from microbial metabolism, for example, are key sources of energy for intestinal epithelial cells of host and gut microbiota [269,270]. SCFAs play a vital role in homeostasis regulation via influencing epigenetic processes [271–274]. Propionate and acetate are the most prevalent SCFAs in the colon. Several *Negativicutes* and *Bacteroides* mostly create propionate via the succinate cascade [275]. Butyrate can trigger colonic Treg cell development in mice and increase acetylation of histone H3 in the repetitive introns and Foxp3 promoter [86]. Butyrate, an essential source of energy for IECs, may be produced by *Firmicutes* via the acetate CoA-transferase cycle from butyryl-CoA [269,276,277]. Amino acid and peptide fermentation can also produce butyrate and propionate. Both promote the hyperacetylation of specific transcription factors involved in signal transduction and histones, which inhibits activity of HDAC in IECs and immune cells; as a result, they play an important part in cancer formation [278]. By current absorption, electroneutralization or passive diffusion, propionate and acetate are consumed by colon cells and transferred to peripheral organs. It has been demonstrated experimentally that the levels of SCFAs in the intestinal contents of germ-free mouse are lesser than in ordinary animals [166]. The levels of SCFAs in faeces may not properly signify the rate of formation of SCFAs in the intestinal lumen, as the majority of SCFAs may be consumed by the host [167]. Several microbial species, such as *Eggerthella lenta*, *Eubacterium limosum*, *Clostridium* and *Bacteroides* may be able to biotransform certain aromatic SCFA derivatives, such as phenylbutyrate and phenylacetate [279] (Table 4).

9. Targeting epigenetics using terahertz radiation

Non-ionizing terahertz (THz) rays in the sunlight spectrum (wavelength $\lambda = 1$ mm–0.1 mm) have shown great potential for a range of biochemical uses in past decades [303], since they could permeate deep into tissue without causing any harm or damage to live beings [304]. In particular, non-thermal THz waves (THzWs) can produce methylation of promoter regions in DNA, which modulates expression of genes without

Table 3
Food sources as a source to target epigenetics.

Name of product	Food source	Class	Epigenetic alterations	Phenotypic alteration	Reference
Triptolide	Tripterygium wilfordi/ thunder god vine	Terpenoids	H3 acetylation is reduced globally, but histone methylation is increased. Expressions of miR-17-92 and miR-193b-3p are altered.	Inhibits metastasis by arresting the cell cycle and inducing apoptosis.	[216,217]
Thymoquinone	Black cumin	Terpenoids	DNMT1 is induced/disrupted. Controls histone acetylation and deacetylation. MiR-34a is upregulated, while miR206b-3p and miR146a are downregulated.	Reduces cell growth, prevents cell cycle progression, and inhibits metastasis.	[218,219]
Sulforaphane (SFN)	Sprouts, broccoli, cabbage	Isothiocyanate	Reduces the expression of HDAC4, HDAC3, HDAC2, and HDAC1 proteins. Reduced expression of miR-21, miR155, miR-145, miR143, DNMT3B, DNMT1	Induction of apoptosis and autophagy, as well as cell cycle arrest (CCA) and death	[220]
Retinoic acid	Vegetables, sweet potatoes, palm oil, orange root, orange and yellow fruits	Vitamin A	DNMT1 and 3 are repressed, whereas methylation of histone and expression of HAT are increased. MiR-10a is influenced.	Reduces cell growth while increasing apoptotic and cancer cell death.	[221,222]
Resveratrol	Grape, mulberries, peanuts	Polyphenol	DNMT and HDAC inhibitor targets HATs, and modify miRNAs such as miR27, miR-106b-25, miRNA-182, miR-1305 and others.	Apoptosis activation, mitophagy, cell cycle disruption, decreased TMZ resistance	[223–225]
Quercetin	Onion, citrus	Flavanoids	DNMT1, HAT and HDAC1 are inhibited, whereas let-7c, miR-16 and miR-217 are regulated.	Proliferation is inhibited, the cell cycle is inhibited, apoptosis is activated, and mitophagy	[226,227]
Piceatannol	Berries, grapes	Polyphenol (stilbene)	DNMT3 levels are reduced, miR129 expression is increased, and miR-21 is regulated.	Reduces cell growth by causing apoptotic cell death.	[228]
Phenyl isothiocyanate (PEITC)	Cruciferous vegetables, watercress	Isothiocyanate	Inhibits HDAC, controls miR135a, miR-194, and miR-192, and modulates acetylation and methylation.	Reduces EMT by causing cell death and activating apoptotic genes.	[229,230]
Parthenolide	*Tanacetum parthenium*	Terpenes	DNMT1 and HDAC1 activity is inhibited.	Anti-proliferative, promotes apoptosis, anti-inflammatory, suppresses cell cycle, and inhibits metastasis	[186,231]
Organosulfur compounds	Chives, garlic		HDACs are inhibited, whereas HATs are increased.	Antiangiogenesis, pro-apoptotic, inhibits proliferation, recruitment, and infiltration.	[232,233]
Lycopene	Tomatoes	Terpenoid	Changes miRNA-21 and suppresses DNMT3 expression.	Controls damage to DNA and tumor development, as well as managing cell division and death.	[234,235]
Kaempferol	Leek, apples, carrots	Flavonoid	Expression of HDAC is restricted, DNMT 3b is reduced, miR-21 is downregulated, and miR-340 is upregulated.	Cell growth is inhibited, resulting in CCA and death.	[236]
Indole-3-carbinol	Cruciferous vegetables	Glucosinolates	Class 1 HDACs are degraded, whereas Class 2 HDACs are increased. Different HDAC expression influences miRNA expression differently, such as miR34a and miR-146b.	It inhibits tumor development by inducing apoptosis, CCA and cell death.	[237,238]
Icariin	*Herba epimedii*	Flavonoids	Acetylation of H4, decreased expression of miR-21 and miR-625-3p.	Cell growth is reduced, apoptosis is induced, and recruitment and infiltration are reduced.	[239]
Gossypol	Cotton plant	Phenol	Reduces HDAC, modifies HMT, and regulates miRNAs such as miR-125b and miR-15a.	Tumor growth inhibition, mitophagy, autophagy, cell death	[240,241]
Genistein	Soybean	Soy polyphenols	Histone changes occur as methylation levels rise or fall. Modulates miRNAs such as miR221/miR-222, miR-15b and miR-125b along with increasing expression of HAT.	Mitophagy, nucleation complex, cell growth restriction, apoptosis and regulation of cell cycle	[242]
Garcinol	Lemon drop mangosteen	Phenol	Acetylation of histone is inhibited, with varied effects on let-7, miR-218, miR-205, miR-200, H4 and H3.	Reverses EMT by inhibiting cell proliferation and increasing apoptosis.	[240,243,244]
Epigallocatechin-3-gallate (EGCG)	Green tea	Polyphenol (stilbene)	Decrease methylation of promoter, reduces DNMT 3b, DNMT 3a and DNMT 1 and controls miR-16, miR-210 and let-7a.	Formation of phagophore, reduction of metastasis and invasion, and restriction of cell cycle progression, growth, and division.	[242,245,246]
Curcumin	Turmeric	Phenol	Inhibitor of DNMT. Decreases expression of HDAC8, HDAC3 and HDAC1. Modulator of miR-34a and miR17-92.	Maturation of APH, mitophagy, inhibition of angiogenesis and activation of apoptosis	[247,248]
Cucurbitacin B	Cucumber	Triterpenoid	DNMTs and HDACs are degraded and regulated, acetylation of histone is increased, miR146-5p and miR-143 and are altered.	Cell apoptosis is induced by anti-proliferative cytoskeleton disruption.	[249,250]
Berberine	Oregano, grape, barberry	Alkaloid	DNMT1 and 3 are inhibited and miR-21, miR23a, miR203 and miR429 are restored.	Causes apoptosis, inhibits cell proliferation, inhibits recruitment and infiltration and inhibits tumor development	[251–253]
Apigenin	Parsley, orange onion	Flavonoids	Decreases HDAC3 and HDAC1, suppresses hypermethylation and DNMT and differently modulates miRNAs such as miR-125a5p and miR138.	Inhibits cell proliferation by causing CCA and death.	[172]
Allyl isothiocyanate (AITC)	Mustard, cabbage, broccoli	Isothiocyanate	Lysine acetylation, methylation, miR-155 and p21 reactivation are all regulated.	Induction of apoptosis, suppression of metastatic spread, and reduction of proinflammatory indicators.	[220,254]

Table 4
Gut microbiota and associated metabolites to target epigenetics.

Gut microbiota and associated metabolites	Epigenetic alterations	Reported mechanisms	Outcomes	References
Propionate Acetate	HDAC3 HDAC2	HDAC3 and HDAC2 inhibition	Nm	[280]
Lactobacillus plantarum Akkermansia muciniphila	N6-methyladenosine alteration	Mettl16 expression and the mRNA that encodes S-adenosylmethionine synthase Methylation of Mat2a.	Influence the host's antibacterial defences, inflammation and metabolism.	[281]
Butyrate	Hypomethylation of LINE1 and FFAR3	LINE1 and FFAR3 DNA methylation	Metabolic disorders are influenced.	[282]
	H3K27me3	The enrichment of H3K27me3 is inversely linked to the down-regulation of NFκB1 dependent on concentration.	In colon tissues, H3K27me3 of the NFκB1 promoter is elevated, which reduces inflammation of intestine.	[283]
	Downregulation of miR-24	To withstand caspase inhibition, reduces the expression of XIAP.	Cancer cell death	[283]
	Reduces the concentrations of miR-17-92a.	Butyrate suppresses transcription of miR-92a via decreasing c-Myc protein production, which is regulated by the interaction between the c-Myc and C12or f25 promoter, hence increasing p57 levels.	Suppresses colon cancer cell proliferation and apoptosis; increases apoptosis	[284]
	HDAC2, HDAC1 inhibition	Hyperacetylation of histones along with transcription of genes are induced.	Inhibits cell proliferation, promotes differentiation and treats cancer.	[283]
	Inhibition of HDAC3	Increase intestinal macrophage antibacterial activity; reduce HDAC3 activity in IECs.	Increase resistance of intestine against infections; avoid obesity induced by diet.	[285,286]
Butyrate and propionate	Inhibition of HDAC	Suppresses *Prdm1* and *Aicda* in B cells by downregulating their mRNA-3'UTRs.	Inhibit autoantibody synthesis and autoimmunity in lupus erythematosus mice.	[287]
Catechins	DNMT1 expression in the colon is increased.	Inhibition of DNMT activity by degrading catechins to form phenolic acids.	Inhibition of growth of the tumor tissues.	[288,289]
Lactobacillus johnsonii 129 and *Bacteroides acidifaciens* type A43	MiR-21-5p	ARF4 controls intestinal epithelial permeability via commensal microbiome-dependent expression of miR-21-5p in IECs.	Regulation of epithelial permeability in the intestine.	[290]
Fusobacterium nucleatum	miRNAs, TLR	Reduces the expression of miR-18a * and miR-4802, resulting in the depressurization of proteins related to autophagy ATG7 and ULK1.	Lowers cancer recurrence by improving chemo-response.	[291]
Gutmicrobiota	HDAC3	Promote lipid absorption and dietary-induced obesity by programming diurnal metabolic cycles, coactivating ERRα transcription of the lipid transporter gene CD36.	Induction of microbiota-dependent rhythmic	[292]
	MicroR-107	Affects the activation of the NF-κB and MyD88 mechanisms; targets IL-23p19 expression of genes.	Gut homeostasis maintenance and IBD treatment.	[293]
	Acetylation of H3 histones	Improves the acetylation of H3 histones in the Foxp3 promoter and protect introns.	Nm	[283]
	Methylation of DNA	DNMT1 may be activated by metabolites, and the methylation of three 'CpG islands' may then be regulated.	Advantage to epithelial cell maturation.	[294]
Inositol-1,4,5- trisphosphate	Activation of HDAC3	Butyrate has an antagonistic influence on HDAC3.	Promotes epithelial healing by activating histone deacetylase in IECs.	[295]
Lactobacilli	Downregulation of miRNAs	Nm	Maintenance of homeostasis and influencing the infectious response of the host	[296]
Leuconostoc mesenteroides	miRNA-200b, miRNA-21		Stimulates colon cancer cells to die through apoptosis.	[283]
Listeria monocytogenes	IL8 promoter, histone H4, histone H3	In HUVEC cells, recruiting of the histone acetylate cyclic adenosine 3, phosphorylation/acetylation of histone H3 and H4.	Nm	[202,290]
LPS	Methylation of TL4	Reduced transcriptional activity at this region results in reduced LPS responses.	Activation of innate immune system	[297]
Methionine	Methylation of DNA	Generation of substrates for production of SAM	Microbiota formation in the host; microbiota metabolism regulation	123, 124
Mycobacterium tuberculosis		Demethylation can be induced by oxidising 5mC to 5hmC through proteins of TET family.	Enhanced chromatin availability, immune transcription factors and activated histone marker sites	[298]
Salmonella enterica, Helicobacter pylori and *Mycobacterium tuberculosis*	MiR-let-7f	By secreting ESAT-6, *M. tuberculosis* reduces the expression of miR-let-7 f. Mir-let-7f inhibits TNFAIP3 which is a negative regulator of the NF-κB pathway.	Activation of the immune system of the host and decrease bacteria survival.	[283]
Polyamines (putrescine, spermidine, arginine)	DNMT, methylation of DNA	Increase dcAdoMet to suppress DNMT activity and repair systemic DNA methylation abnormalities.	Cancer treatment might be possible.	[283]
SCFAs	Activation and inhibition of Stat3 and HDACs, respectively.	Claudin-2 inhibition, which is a method dependent on IL-10RA.	Support the development of an epithelial barrier.	[299]
	Nuclear SIRT1	Produce resveratrol derivatives and enhance its accessibility by using precursors.	Aging, genomic stability, metabolism, mitochondrial biogenesis, stress responses are all regulated.	[283]
	SLC5A8	SLC5A8 enhances butyrate entry into cells and inhibits HDACs as a plasma membrane transporter of SCFAs.	Cancer cell death	[283]

(*continued on next page*)

Table 4 (*continued*)

Gut microbiota and associated metabolites	Epigenetic alterations	Reported mechanisms	Outcomes	References
	H3K4me3 histone, GPR43	Binds to the promoter regions of inflammatory repressors and inhibits the cAMP-PKA-CREB expression level that contributes to HDAC overexpression.	Prevents against colon cancer by regulating colonic inflammation.	[300]
	HDAC3	Co-activation of ERRα	Promote fat absorption and diet-induced obesity by programming diurnal metabolic cycles.	[292]
	GPCRs, HDACs	Inhibits HDACs and boosts acetylation of FOXP3 protein and expression of genes in $CD4^{+}$T cells, increases Treg cell development in the extrathymic, and stimulates the production of GPCRs, β-defensin-2 and 3, represses STAT1 and NF-κB activation.	Anti-inflammatory action	[283]
pABA, DHPP and Vitamins	HMTs, DNMTs	Produces SAM, a methyl-donating substrate for HMTs and DNMTs.	Nm	[301,302]

causing any sequencing changes which is due to ROS production along with DNA damage [305]. As a result, many genes that are inhibited by chemotherapy or phototherapy can be selectively suppressed [306,307]. Non-thermal THzW selective methylation at the promoter site of nuclear factor-erythroid factor 2-related factor 2 (NRF2), a significant gene that inhibits chemotherapy in most malignancies by activating basic antioxidant responsive genes [308]. Transactivation of genes involved in transcription, synthesis, repair and methylation of DNA and cell cycle control occurs when intracellular signalling pathways are activated in response to THz rays. Different epigenetic medicines combined with several rays, notably ultraviolet radiation (UVR), improve cancer chemotherapeutic results [304,307,309]. Understanding the complexities of mechanisms of oxidative stress (OS) that regulate tumor progression, melanocyte proliferation and pigmentation suggests the possibility to identify a multitude of therapeutically effective rays that hold significant potential for patients with skin disorders. As per the stimulation of certain gene products, the actions of THz rays on expression of genes may be characterised as early or late effects; these THz reactions are critical in affecting fate of the cell, such as apoptosis, cell survival and growth arrest. THz is considered to produce a certain amount of ROS, which might trigger apoptosis and other cellular signalling mechanisms. Because of their powerful cytoprotective actions under stressed conditions, the NRF2 and heme oxygenase-1 (HO-1) antioxidative pathways are assumed to represent the key barrier in chemotherapy drugs. However, it has recently been revealed that NRF2 may exacerbate this OS, eventually resulting in cell death [272].

10. Epigenetics modification using cold atmospheric plasma

Cold atmospheric pressure plasma (CAP) is an ionised medium containing mostly ROS and reactive nitrogen species (RNS) [310]. CAP has received interest for medicinal uses, particularly cancer therapy, as it was effectively manufactured under cold circumstances [311]. In fact, in a variety of cancer types, CAP has been shown to suppress cancer cell development differently than its normal equivalent. By causing double-strand breaks (DSBs) in the DNA, CAP may cause a genetic alteration in the nucleus. DSBs were seen in CAP-treated lung cancer cells, resulting in cell death [312]. Although CAP was found to generate DSBs in leucocytes implanted in agarose, it is unknown if it may directly generate DSBs in the cell [313]. Apart from DSBs, nothing is understood about gene mutations in DNA at the base level like nucleotide mutation. Epigenetic mechanisms such as histone modification, miR and CpG methylation have emerged as an alternative explanation for the varied alterations in gene expression and cellular activity caused by CAP [314]. According to Lee et al. (2016), CAP therapy resulted in hypermethylation and down-regulation of miR-19a, an oncomiR, as well as up-regulation of miR-19a target genes in MCF-7 breast cancer cells. Furthermore, CAP inhibited the cell proliferation impact caused by miR-19a upregulation. These findings might help to identify the epigenetic mechanisms of CAP when it is given to cells and tissues for cancer therapy.

11. Targeting epigenetic machinery with nanotechnology

Despite constant advancements, epigenetic medicine still confronts significant hurdles. Epigenetic medicines currently authorized by the USFDA lack locus sensitivity and are non-selective in blocking distinct HDAC and DNMTs isozymes. Because of this, unwanted off-target events arise, resulting in severe drug toxicity and inability to elicit long-term response [66]. Furthermore, these epigenetic medications' limited permeability and solubility, along with their poor pharmacokinetic features, like lack of bioavailability and stability, are substantial barriers to their wider clinical uses [315]. In order to fully utilize the therapeutic potential of these medications, it is critical to improve drug delivery efficiency, increase drug stability and optimize target specificity. Because nanoscale delivery methods and prodrugs can promote tumor-targeted administration and cellular internalisation, boost bioavailability and guard against early hydrolysis, also they have the capacity to treat some of the therapeutic difficulties that currently exist with epigenetic drugs [316]. Second-generation nucleoside analogues are now being evaluated to overcome the tolerability and stability problems [66]. Combining NPs packed with epigenetic-targeted drugs with chemotherapeutic drugs is evolving as a viable technique for achieving more therapeutic advantages while minimising negative effects [66,317]. Despite the fact that multiple clinical trials have demonstrated the potential of using NP delivery systems to target siRNAs in tumors and investigate their clinical efficacy in cancer treatment, further research is required to investigate bio - compatibility and pharmacokinetic profiles and effectiveness of current delivery carriers [318].

Epigenetic effect of nanomaterials is described in Fig. 5 in which they start cellular signalling which leads to genotoxicity, lipids peroxidation, cytotoxicity, apoptosis, miRNAs dysregulation along with altered expression of gene [319].

11.1. Conclusion and future perspectives

Even though more precise mechanisms must be researched, it is commonly known that epigenetic activities are critical in both normal biochemical mechanisms and tumor pathways, and that epigenetic status is often greatly changed during cancer onset. As a result, epigenome-targeted therapy appears to be a potential option for cancer therapy. Because of the complexities of cancer, epigenetic changes have affected a range of cancer properties, including oncogene expression along with tumor repressor genes, as well as cell signalling, that results in rapid cancer growth, infiltration, and metastases. There are several strategies and advancement to target epigenetic machinery. These include combination therapy, adjuvant therapy, and probiotics, CRISPR Cas-9 editing, phytochemicals, Phototherapy, cold atmospheric plasma, nanocarriers and terahertz rays. All these novel therapeutic strategies lead to tackle drug resistance along with better treatment option with

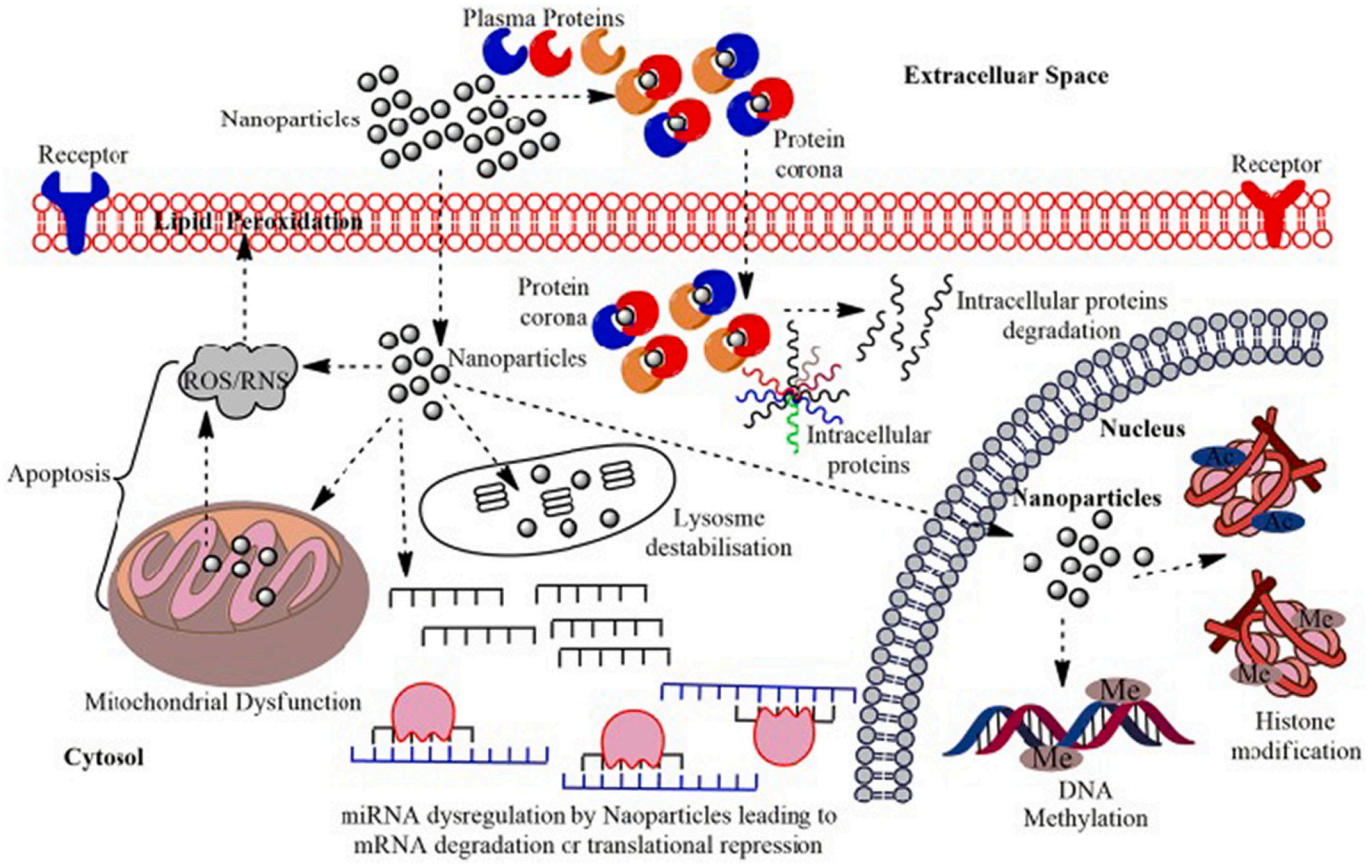

Fig. 5. Epigenetic effect of nanomaterials, NPs induce cytotoxicity, Interact with mitochondria for the production of oxidative stress which leads to apoptosis through lipid peroxidation. Dysregulated of miRNA causes altered expression associated proteins and genes. Epigenetic effects in the cell are caused by these metallic and non-metallic NPs which cause DNA methylation and histone modification [319].

high rate of cure and recovery. Epigenetic targeting appears to be a potential anticancer therapeutic method based on the results achieved. Many features of cancer onset are associated with epigenomes. It is required to have a deeper knowledge of the exact processes behind such modifications in various cancers. Meanwhile, improved therapy approaches, including a range of combinations, have yet to be developed. Epigenetic modifications lead to chemo-resistance. Hence it is necessary to consider epigenetic machinery while treating cancer. Terahertz rays and cold atmospheric plasma are novel targets and it is the need of hour to perform more research on these novel tools. Bacteria based therapy or probiotics is also very hot topic since 2020 in the field of oncology that is why their adjuvant and combination therapeutics would gain much attention in the future with high cure rate. More work is required on phytochemicals and CRISPR based therapy to deal with epigenetic alterations in cancer [212].

Declaration of competing interest

The manuscript is solely submitted to BBA Reviews on Cancer and authors have not conflict of interest.

Data availability

No data was used for the research described in the article.

Acknowledgments

N.D.T. and H.T. acknowledge that the project leading to this research has received funding from the European Union's Horizon 2020 Research and Innovation Programme under the Marie Sklodowska-Curie Grant Agreement No. 840964 'SUPERBRAIN'. This publication is based upon work from COST Action CA 17140 "Cancer Nanomedicine from the Bench to the Bedside" supported by COST (European Cooperation in Science and Technology).

References

[1] W. Zhang, J. Qu, G. Liu, JJNrMcb Belmonte, in: The Ageing Epigenome and Its Rejuvenation 21, 2020, pp. 137–150.
[2] J.-H. Lee, et al., Heterochromatin: an epigenetic point of view in aging, Exp. Mol. Med. 52 (9) (2020) 1466–1474.
[3] S. Pal, J.K. Tyler, Epigenetics and aging, Science Adv. 2 (7) (2016), e1600584.
[4] A.P. Feinberg, M.A. Koldobskiy, A. Göndör, Epigenetic modulators, modifiers and mediators in cancer aetiology and progression, Nat. Rev. Genet. 17 (5) (2016) 284–299.
[5] P.A. Jones, S.B. Baylin, The fundamental role of epigenetic events in cancer, Nat. Rev. Genet. 3 (6) (2002) 415–428.
[6] J.S. You, P.A. Jones, Cancer genetics and epigenetics: two sides of the same coin? Cancer cell 22 (1) (2012) 9–20.
[7] J.-P.J. Issa, H.M. Kantarjian, Targeting DNA methylation, Clin. Cancer Res. 15 (12) (2009) 3938–3946.
[8] S. Feng, D.D. De Carvalho, Clinical advances in targeting epigenetics for cancer therapy, FEBS J. 5 (289) (2021) 1214–1239.
[9] A. Majchrzak-Celińska, A. Warych, M. Szoszkiewicz, Novel approaches to epigenetic therapies: from drug combinations to epigenetic editing, Genes 12 (2) (2021) 208.
[10] H.-C. Tsai, S.B. Baylin, Cancer epigenetics: linking basic biology to clinical medicine, Cell Res. 21 (3) (2011) 502–517.
[11] P.A. Jones, S.M. Taylor, Cellular differentiation, cytidine analogs and DNA methylation, Cell 20 (1) (1980) 85–93.
[12] P.A. Jones, S.M. Taylor, Hemimethylated duplex DNAs prepared from 5-azacytidine-treated cells, Nucleic Acids Res. 9 (12) (1981) 2933–2947.
[13] A. Aparicio, J.S. Weber, Review of the clinical experience with 5-azacytidine and 5-aza-2'-deoxycytidine in solid tumors, Curr. Opin. Investig. Drugs (London, England: 2000) 3 (4) (2002) 627–633.

[14] J. Ma, Z. Ge, Comparison between decitabine and azacitidine for patients with acute myeloid leukemia and higher-risk myelodysplastic syndrome: a systematic review and network meta-analysis, Front. Pharmacol. (2021) 1919.
[15] S.R. Bohl, L. Bullinger, F.G. Rücker, Epigenetic therapy: azacytidine and decitabine in acute myeloid leukemia, Expert. Rev. Hematol. 11 (5) (2018) 361–371.
[16] K.E. Bachman, M.R. Rountree, S.B. Baylin, Dnmt3a and Dnmt3b are transcriptional repressors that exhibit unique localization properties to heterochromatin, J. Biol. Chem. 276 (34) (2001) 32282–32287.
[17] M.R. Rountree, K.E. Bachman, S.B. Baylin, DNMT1 binds HDAC2 and a new co-repressor, DMAP1, to form a complex at replication foci, Nat. Genet. 25 (3) (2000) 269–277.
[18] A. Quagliano, A. Gopalakrishnapillai, S.P. Barwe, Understanding the mechanisms by which epigenetic modifiers avert therapy resistance in cancer, Front. Oncol. 10 (2020) 992.
[19] S. Patnaik, Drugs targeting epigenetic modifications and plausible therapeutic strategies against colorectal cancer, Front. Pharmacol. 10 (2019) 588.
[20] T. Qin, et al., Mechanisms of resistance to 5-aza-2′-deoxycytidine in human cancer cell lines, Blood 113 (3) (2009) 659–667.
[21] S. Keyvani-Ghamsari, et al., Current understanding of epigenetics mechanism as a novel target in reducing cancer stem cells resistance, Clin. Epigenetics 13 (1) (2021) 1–31.
[22] S.D. Gore, et al., Impact of the putative differentiating agent sodium phenylbutyrate on myelodysplastic syndromes and acute myeloid leukemia, Clin. Cancer Res. 7 (8) (2001) 2330–2339.
[23] R.L. Piekarz, et al., Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma, J. Clin. Oncol. 27 (32) (2009) 5410.
[24] M. Duvic, C. Zhang, Clinical and laboratory experience of vorinostat (suberoylanilide hydroxamic acid) in the treatment of cutaneous T-cell lymphoma, Br. J. Cancer 95 (1) (2006) S13–S19.
[25] S.V. Sharma, et al., A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations, Cell 141 (1) (2010) 69–80.
[26] E.E. Cameron, et al., Synergy of demethylation and histone deacetylase inhibition in the re-expression of genes silenced in cancer, Nat. Genet. 21 (1) (1999) 103–107.
[27] S.D. Gore, et al., Combined DNA methyltransferase and histone deacetylase inhibition in the treatment of myeloid neoplasms, Cancer Res. 66 (12) (2006) 6361–6369.
[28] W. Blum, et al., Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia, J. Clin. Oncol. 25 (25) (2007) 3884–3891.
[29] J.-P.J. Issa, et al., Phase 1 study of low-dose prolonged exposure schedules of the hypomethylating agent 5-aza-2′-deoxycytidine (decitabine) in hematopoietic malignancies, Blood 103 (5) (2004) 1635–1640.
[30] H. Kantarjian, et al., Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study, Cancer 106 (8) (2006) 1794–1803.
[31] A. Nebbioso, et al., Cancer epigenetics: moving forward, PLoS Genet. 14 (6) (2018), e1007362.
[32] D. Morel, et al., Combining epigenetic drugs with other therapies for solid tumours—past lessons and future promise, Nat. Rev. Clin. Oncol. 17 (2) (2020) 91–107.
[33] L. Villanueva, D. Álvarez-Errico, M. Esteller, The contribution of epigenetics to cancer immunotherapy, Trends Immunol. 41 (8) (2020) 676–691.
[34] K.T. Thurn, et al., Rational therapeutic combinations with histone deacetylase inhibitors for the treatment of cancer, Future Oncol. 7 (2) (2011) 263–283.
[35] A.P. Bird, A.P.J.C. Wolffe, in: Methylation-induced Repression—Belts, Braces, and Chromatin 99, 1999, pp. 451–454 (5).
[36] E.E. Cameron, et al., in: Synergy of Demethylation and Histone Deacetylase Inhibition in the Re-expression of Genes Silenced in Cancer 21, 1999, pp. 103–107, 1.
[37] W.-G. Zhu, G.A. Otterson, The Interaction of histone deacetylase inhibitors and DNA methyltransferase inhibitors in the treatment of human cancer cells, Curr. Med. Chem.: Anti-Cancer Agents 3 (3) (2003) 187–199.
[38] C.L. Glasser, et al., in: Epigenetic Combination Therapy for Children With Secondary Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) and Concurrent Solid Tumor Relapse 39, 2017, p. 560, 7.
[39] R.A. Juergens, et al., in: Combination Epigenetic Therapy Has Efficacy in Patients With Refractory Advanced Non–small Cell Lung Cancer 1, 2011, pp. 598–607, 7.
[40] C.R. Klaus, et al., in: DOT1L Inhibitor EPZ-5676 Displays Synergistic Antiproliferative Activity in Combination With Standard of Care Drugs and Hypomethylating Agents in MLL-rearranged Leukemia Cells 350, 2014, pp. 646–656, 3.
[41] F.V. Pericole, et al., in: BRD4 Inhibition Enhances Azacitidine Efficacy in Acute Myeloid Leukemia and Myelodysplastic Syndromes 9, 2019, p. 16.
[42] M. Christmann, B. Kaina, Epigenetic regulation of DNA repair genes and implications for tumor therapy, Mutat. Res. Rev. Mutat. Res. 780 (2019) 15–28.
[43] N. Hajji, et al., The bitter side of epigenetics: variability and resistance to chemotherapy, Epigenomics 13 (05) (2021) 397–403.
[44] S. Vural, et al., Association of expression of epigenetic molecular factors with DNA methylation and sensitivity to chemotherapeutic agents in cancer cell lines, Clin. Epigenetics 13 (1) (2021) 1–23.
[45] P.A. Jones, J.-P.J. Issa, S.J.N.R.G. Baylin, in: Targeting the Cancer Epigenome for Therapy 17, 2016, pp. 630–641, 10.
[46] L. Ponnusamy, P.K.S. Mahalingaiah, K.P. Singh, Epigenetic reprogramming and potential application of epigenetic-modifying drugs in acquired chemotherapeutic resistance, Adv. Clin. Chem. 94 (2020) 219–259.
[47] C.C. Bell, O. Gilan, Principles and mechanisms of non-genetic resistance in cancer, Br. J. Cancer 122 (4) (2020) 465–472.
[48] S. Romero-Garcia, H. Prado-Garcia, A. Carlos-Reyes, Role of DNA methylation in the resistance to therapy in solid tumors, Front. Oncol. 10 (2020) 1152.
[49] T. Clozel, et al., in: Mechanism-based Epigenetic Chemosensitization Therapy of Diffuse Large B-cell Lymphoma 3, 2013, pp. 1002–1019, 9.
[50] B. Pera, et al., in: Combinatorial Epigenetic Therapy in Diffuse Large B Cell Lymphoma Pre-clinical Models and Patients 8, 2016, pp. 1–10, 1.
[51] C. Fischer, et al., in: Panobinostat Reduces Hypoxia-induced Cisplatin Resistance of Non-small Cell Lung Carcinoma Cells via HIF-1α Destabilization 14, 2015, pp. 1–16 (1).
[52] K. Xue, et al., in: Vorinostat, a Histone Deacetylase (HDAC) Inhibitor, Promotes Cell Cycle Arrest and Re-sensitizes Rituximab-and Chemo-resistant Lymphoma Cells to Chemotherapy Agents 142, 2016, pp. 379–387, 2.
[53] K. Graham, E. Unger, Overcoming tumor hypoxia as a barrier to radiotherapy, chemotherapy and immunotherapy in cancer treatment, Int. J. Nanomedicine 13 (2018) 6049.
[54] J.A. Moscow, T. Fojo, R.L. Schilsky, The evidence framework for precision cancer medicine, Nat. Rev. Clin. Oncol. 15 (3) (2018) 183–192.
[55] Y. Viossat, R. Noble, A theoretical analysis of tumour containment, Nat. Ecol. Evol. 5 (6) (2021) 826–835.
[56] A. Levitzki, S. Klein, My journey from tyrosine phosphorylation inhibitors to targeted immune therapy as strategies to combat cancer, Proc. Natl. Acad. Sci. 116 (24) (2019) 11579–11586.
[57] L. Zhong, et al., Small molecules in targeted cancer therapy: advances, challenges, and future perspectives, Signal Transduct. Target. Ther. 6 (1) (2021) 1–48.
[58] C.M. Lovly, A.T. Shaw, Molecular pathways: resistance to kinase inhibitors and implications for therapeutic strategies, Clin. Cancer Res. 20 (9) (2014) 2249–2256.
[59] R. Vander Velde, et al., Resistance to targeted therapies as a multifactorial, gradual adaptation to inhibitor specific selective pressures, Nat. Commun. 11 (1) (2020) 1–13.
[60] H.-M. Zhou, et al., Targeting cancer stem cells for reversing therapy resistance: mechanism, signaling, and prospective agents, Signal Transduct. Target. Ther. 6 (1) (2021) 1–17.
[61] P. Ramos, M. Bentires-Alj, Mechanism-based cancer therapy: resistance to therapy, therapy for resistance, Oncogene 34 (28) (2015) 3617–3626.
[62] N. Vasan, J. Baselga, D.M. Hyman, A view on drug resistance in cancer, Nature 575 (7782) (2019) 299–309.
[63] A.J. Sabnis, T.G. Bivona, Principles of resistance to targeted cancer therapy: lessons from basic and translational cancer biology, Trends Mol. Med. 25 (3) (2019) 185–197.
[64] S.P. Angus, et al., in: Epigenetic Mechanisms Regulating Adaptive Responses to Targeted Kinase Inhibitors in Cancer 58, 2018, pp. 209–229.
[65] Y. Cheng, et al., Targeting epigenetic regulators for cancer therapy: mechanisms and advances in clinical trials, Signal Transduct. Target. Ther. 4 (1) (2019) 1–39.
[66] A. Roberti, et al., Epigenetics in cancer therapy and nanomedicine, Clin. Epigenetics 11 (1) (2019) 1–18.
[67] T. Yang, Y. Yang, Y. Wang, Predictive biomarkers and potential drug combinations of epi-drugs in cancer therapy, Clin. Epigenetics 13 (1) (2021) 1–19.
[68] M. Chen, et al., in: The HDAC Inhibitor, MPT0E028, Enhances Erlotinib-induced Cell Death in EGFR-TKI-resistant NSCLC Cells 4, 2013, p. e810, 9.
[69] T.G. Lee, et al., in: The combination of irreversible EGFR TKI s and SAHA induces apoptosis and autophagy-mediated cell death to overcome acquired resistance in EGFR T 790 M-mutated lung cancer 136, 2015, pp. 2717–2729, 11.
[70] L.H. Dong, et al., in: Histone Deacetylase Inhibitor Potentiated the Ability of MTOR Inhibitor to Induce Autophagic Cell Death in Burkitt Leukemia/Lymphoma 6, 2013, pp. 1–11, 1.
[71] B.R. Beagle, et al., in: mTOR Kinase Inhibitors Synergize With Histone Deacetylase Inhibitors to Kill B-cell Acute Lymphoblastic Leukemia Cells 6, 2015, p. 2088 (4).
[72] M. Zibelman, et al., in: Phase I Study of the mTOR Inhibitor Ridaforolimus and the HDAC Inhibitor Vorinostat in Advanced Renal Cell Carcinoma and Other Solid Tumors 33, 2015, pp. 1040–1047, 5.
[73] M. Konopleva, et al., in: Efficacy and Biological Correlates of Response in a Phase II Study of Venetoclax Monotherapy in Patients With Acute Myelogenous Leukemia 6, 2016, pp. 1106–1117, 10.
[74] P. Bose, et al., in: Pathways and Mechanisms of Venetoclax Resistance 58, 2017, pp. 2026–2039, 9.
[75] T. Tsao, et al., in: Concomitant Inhibition of DNA Methyltransferase and BCL-2 Protein Function Synergistically Induce Mitochondrial Apoptosis in Acute Myelogenous Leukemia Cells 91, 2012, pp. 1861–1870, 12.
[76] C.D. DiNardo, et al., in: Venetoclax Combined With Decitabine or Azacitidine in Treatment-naive, Elderly Patients With Acute Myeloid Leukemia 133, 2019, pp. 7–17, 1.
[77] C. Robert, A decade of immune-checkpoint inhibitors in cancer therapy, Nat. Commun. 11 (1) (2020) 1–3.
[78] J.B. Jacob, M.K. Jacob, P. Parajuli, Review of immune checkpoint inhibitors in immuno-oncology, in: Advances in Pharmacology, Elsevier, 2021, pp. 111–139.
[79] S. Bagchi, R. Yuan, E.G. Engleman, Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance, Annu. Rev. Pathol.: Mech. Dis. 16 (2021) 223–249.

[80] M.J. Topper, et al., in: The Emerging Role of Epigenetic Therapeutics in Immuno-oncology 17, 2020, pp. 75–90.
[81] P.A. Jones, et al., Epigenetic therapy in immune-oncology, Nat. Rev. Cancer 19 (3) (2019) 151–161.
[82] M.J. Topper, et al., The emerging role of epigenetic therapeutics in immuno-oncology, Nat. Rev. Clin. Oncol. 17 (2) (2020) 75–90.
[83] Z. Liu, et al., A new trend in cancer treatment: the combination of epigenetics and immunotherapy, Front. Immunol. 13 (2022) 809761.
[84] S. Aspeslagh, et al., Epigenetic modifiers as new immunomodulatory therapies in solid tumours, Ann. Oncol. 29 (4) (2018) 812–824.
[85] G.-F. Luo, et al., Cell primitive-based biomimetic functional materials for enhanced cancer therapy, Chem. Soc. Rev. 50 (2) (2021) 945–985.
[86] I. Cañadas, et al., in: Tumor Innate Immunity Primed by Specific Interferon-stimulated Endogenous Retroviruses 24, 2018, pp. 1143–1150.
[87] L. Wang, et al., in: Decitabine Enhances Lymphocyte Migration and Function and Synergizes With CTLA-4 Blockade in a Murine Ovarian Cancer Model 3, 2015, pp. 1030–1041, 9.
[88] H.E. Ghoneim, et al. (1), in: De Novo Epigenetic Programs Inhibit PD-1 Blockade-mediated T Cell Rejuvenation 170, 2017, pp. 142–157. e19.
[89] N. Luo, et al., in: DNA Methyltransferase Inhibition Upregulates MHC-I to Potentiate Cytotoxic T Lymphocyte Responses in Breast Cancer 9, 2018, pp. 1–11, 1.
[90] N. Daver, et al., in: Efficacy, Safety, and Biomarkers of Response to Azacitidine and Nivolumab in Relapsed/Refractory Acute Myeloid Leukemia: A Nonrandomized, Open-label, Phase II Study 9, 2019, pp. 370–383, 3.
[91] D.M. Woods, et al., in: HDAC Inhibition Upregulates PD-1 Ligands in Melanoma and Augments Immunotherapy With PD-1 Blockade 3, 2015, pp. 1375–1385, 12.
[92] D. Llopiz, et al., in: Enhanced Anti-tumor Efficacy of Checkpoint Inhibitors in Combination With the Histone Deacetylase Inhibitor Belinostat in a Murine Hepatocellular Carcinoma Model 68, 2019, pp. 379–393, 3.
[93] L. Shen, et al., in: Class I Histone Deacetylase Inhibitor Entinostat Suppresses Regulatory T Cells and Enhances Immunotherapies in Renal and Prostate Cancer Models 7, 2012, p. e30815 (1).
[94] R. Pili, et al., in: Immunomodulation by Entinostat in Renal Cell Carcinoma Patients Receiving High-dose Interleukin 2: A Multicenter, Single-arm, Phase I/II Trial (NCI-CTEP# 7870) 23, 2017, pp. 7199–7208 (23).
[95] W.-M. Zhou, et al., Methylation landscape: targeting writer or eraser to discover anti-cancer drug, Front. Pharmacol. 12 (2021), 690057.
[96] A. Ganesan, et al., The timeline of epigenetic drug discovery: from reality to dreams, Clin. Epigenetics 11 (1) (2019) 1–17.
[97] Y. Huang, et al., in: Nullifying Epigenetic Writer DOT1L Attenuates Neointimal Hyperplasia 308, 2020, pp. 22–31.
[98] S. Biswas, M. Rao, Epigenetic tools (the writers, the readers and the erasers) and their implications in cancer therapy, Eur. J. Pharmacol. 837 (2018) 8–24.
[99] T.B. Nicholson, N. Veland, T. Chen, Writers, readers, and erasers of epigenetic marks, in: Epigenetic Cancer Therapy, Elsevier, 2015, pp. 31–66.
[100] A. Yuqing Yang, et al., in: Natural Compound-derived Epigenetic Regulators Targeting Epigenetic Readers, Writers and Erasers 16, 2016, pp. 697–713 (7).
[101] S. Feng, D.D.J.T.F.J.De Carvalho, Clinical Advances in Targeting Epigenetics for Cancer Therapy, 2021.
[102] G. Zhang, S.J.I.l. Pradhan, in: Mammalian Epigenetic Mechanisms 66, 2014, pp. 240–256 (4).
[103] L. Simó-Riudalbas, M. Esteller, Targeting the histone orthography of cancer: drugs for writers, erasers and readers, Br. J. Pharmacol. 172 (11) (2015) 2716–2732.
[104] P.A. Wade, Methyl CpG binding proteins: coupling chromatin architecture to gene regulation, Oncogene 20 (24) (2001) 3166–3173.
[105] Q. Du, et al., Methyl-CpG-binding domain proteins: readers of the epigenome, Epigenomics 7 (6) (2015) 1051–1073.
[106] S. Denslow, P. Wade, The human Mi-2/NuRD complex and gene regulation, Oncogene 26 (37) (2007) 5433–5438.
[107] B.A. Buck-Koehntop, et al., Molecular basis for recognition of methylated and specific DNA sequences by the zinc finger protein kaiso, Proc. Natl. Acad. Sci. 109 (38) (2012) 15229–15234.
[108] G.J. Filion, et al., A family of human zinc finger proteins that bind methylated DNA and repress transcription, Mol. Cell. Biol. 26 (1) (2006) 169–181.
[109] W.A. Pastor, L. Aravind, A. Rao, TETonic shift: biological roles of TET proteins in DNA demethylation and transcription, Nat. Rev. Mol. Cell Biol. 14 (6) (2013) 341–356.
[110] C. Chen, et al., Deciphering arginine methylation: tudor tells the tale, Nat. Rev. Mol. Cell Biol. 12 (10) (2011) 629–642.
[111] M. Schapira, et al., WD40 repeat domain proteins: a novel target class? Nat. Rev. Drug Discov. 16 (11) (2017) 773–786.
[112] R. Sanchez, M.-M. Zhou, The PHD finger: a versatile epigenome reader, Trends Biochem. Sci. 36 (7) (2011) 364–372.
[113] M.A. Dawson, T. Kouzarides, B.J.J.N.E.J.o.M. Huntly, Targeting epigenetic readers in cancer, N. Engl. J. Med. 367 (7) (2012) 647–657.
[114] P. Filippakopoulos, S. Knapp, Targeting bromodomains: epigenetic readers of lysine acetylation, Nat. Rev. Drug Discov. 13 (5) (2014) 337–356.
[115] B.J. Klein, et al., in: Crosstalk Between Epigenetic Readers Regulates the MOZ/MORF HAT Complexes 9, 2014, pp. 186–193, 2.
[116] E. Damiani, et al., in: Targeting Epigenetic 'Readers' With Natural Compounds for Cancer Interception 25, 2020, p. 189, 4.
[117] N.J. Porter, D.W. Christianson, Structure, mechanism, and inhibition of the zinc-dependent histone deacetylases, Curr. Opin. Struct. Biol. 59 (2019) 9.
[118] H. Jing, H. Lin, Sirtuins in epigenetic regulation, Chem. Rev. 115 (6) (2015) 2350–2375.
[119] R.H. Houtkooper, E. Pirinen, J. Auwerx, Sirtuins as regulators of metabolism and healthspan, Nat. Rev. Mol. Cell Biol. 13 (4) (2012) 225–238.
[120] E. Zhao, et al., The roles of sirtuin family proteins in cancer progression, Cancers 11 (12) (2019) 1949.
[121] R.S. Gil, P. Vagnarelli, Protein phosphatases in chromatin structure and function, Biochim. Biophys. Acta, Mol. Cell Res. 1866 (1) (2019) 90–101.
[122] S.L. Tinsley, B.L. Allen-Petersen, PP2A and cancer epigenetics: a therapeutic opportunity waiting to happen, NAR Cancer 4 (1) (2022), zcac002.
[123] B. Hoermann, et al., Dissecting the sequence determinants for dephosphorylation by the catalytic subunits of phosphatases PP1 and PP2A, Nat. Commun. 11 (1) (2020) 1–20.
[124] J.A. Harrigan, et al., Deubiquitylating enzymes and drug discovery: emerging opportunities, Nat. Rev. Drug Discov. 17 (1) (2018) 57–78.
[125] N.A. Snyder, G.M. Silva, Deubiquitinating enzymes (DUBs): regulation, homeostasis, and oxidative stress response, J. Biol. Chem. 297 (3) (2021).
[126] F.E. Reyes-Turcu, K.H. Ventii, K.D. Wilkinson, Regulation and cellular roles of ubiquitin-specific deubiquitinating enzymes, Annu. Rev. Biochem. 78 (2009) 363–397.
[127] X.I. Ambroggio, et al., JAMM: a metalloprotease-like zinc site in the proteasome and signalosome, PLoS Biol. 2 (1) (2004), e2.
[128] J.A. Schmid, et al., Histone ubiquitination by the DNA damage response is required for efficient DNA replication in unperturbed S phase, Mol. Cell 71 (6) (2018) 897–910, e8.
[129] P. Bruno, et al., LSD1: more than demethylation of histone lysine residues, Exp. Mol. Med. 52 (2020) 1–12.
[130] Y. Meng, et al., Jumonji domain-containing protein family: the functions beyond lysine demethylation, J. Mol. Cell Biol. 10 (4) (2018) 371–373.
[131] K. Wang, et al., Role of the epigenetic modifier JMJD6 in tumor development and regulation of immune response, Front. Immunol. (2022) 1043.
[132] S. Yamaguchi, M. Kaneko, M. Narukawa, Approval success rates of drug candidates based on target, action, modality, application, and their combinations, Clin. Transl. Sci. 14 (3) (2021) 1113–1122.
[133] S. Pushpakom, et al., Drug repurposing: progress, challenges and recommendations, Nat. Rev. Drug Discov. 18 (1) (2019) 41–58.
[134] K. Takahashi, et al., Preleukaemic clonal haemopoiesis and risk of therapy-related myeloid neoplasms: a case-control study, Lancet Oncol. 18 (1) (2017) 100–111.
[135] J.J. Naveja, A. Dueñas-González, J.L. Medina-Franco, Drug repurposing for epigenetic targets guided by computational methods, in: Epi-informatics, Elsevier, 2016, pp. 327–357.
[136] T.T. Ashburn, K.B. Thor, Drug repositioning: identifying and developing new uses for existing drugs, Nat. Rev. Drug Discov. 3 (8) (2004) 673–683.
[137] F. Moreira-Silva, et al., in: Repurposing Old Drugs Into New Epigenetic Inhibitors: Promising Candidates for Cancer Treatment? 12, 2020, p. 410 (5).
[138] S.P. Nunes, et al., DNA methylation as a therapeutic target for bladder cancer, Cells 9 (8) (2020) 1850.
[139] F. Moreira-Silva, et al., Repurposing old drugs into new epigenetic inhibitors: promising candidates for cancer treatment? Pharmaceutics 12 (5) (2020) 410.
[140] M. Montalvo-Casimiro, et al., Epidrug repurposing: discovering new faces of old acquaintances in cancer therapy, FrontiersOncology (2020) 2461.
[141] W.J. Lee, B.T.J.C. Zhu, in: Inhibition of DNA Methylation by Caffeic Acid and Chlorogenic Acid, Two Common Catechol-containing Coffee Polyphenols 27, 2006, pp. 269–277, 2.
[142] A. Oodi, et al., in: Harmine, a Novel DNA Methyltransferase 1 Inhibitor in the Leukemia Cell Line 33, 2017, pp. 509–515, 4.
[143] V. Prachayasittikul, et al., in: Exploring the Epigenetic Drug Discovery Landscape 12, 2017, pp. 345–362, 4.
[144] Z. Yuan, et al., in: Development of a Versatile DNMT and HDAC Inhibitor C02S Modulating Multiple Cancer Hallmarks for Breast Cancer Therapy 87, 2019, pp. 200–208.
[145] B. Chatterjee, K. Ghosh, S.R.J.B. Kanade, in: Resveratrol Modulates Epigenetic Regulators of Promoter Histone Methylation and Acetylation that Restores BRCA1, p53, p21CIP1 in Human Breast Cancer Cell Lines 45, 2019, pp. 818–829, 5.
[146] Z.H. Huang, et al., in: Berberine targets epidermal growth factor receptor signaling to suppress prostate cancer proliferation in vitro 11, 2015, pp. 2125–2128, 3.
[147] M.L. Hartman, et al., in: Parthenolide Induces MITF-M Downregulation and Senescence in Patient-derived MITF-Mhigh Melanoma Cell Populations 7, 2016, p. 9026, 8.
[148] S. Venturelli, et al., Resveratrol as a pan-HDAC inhibitor alters the acetylation status of jistone proteins in human-derived hepatoblastoma cells 8, 2013, 8.
[149] A.C. West, R.W. Johnstone, New and emerging HDAC inhibitors for cancer treatment, J. Clin. Invest. 124 (1) (2014) 30–39.
[150] M. Bots, R.W. Johnstone, Rational combinations using HDAC inhibitors, Clin. Cancer Res. 15 (12) (2009) 3970–3977.
[151] C. Arce, et al., in: Hydralazine target: from blood vessels to the epigenome 4, 2006, pp. 1–16, 1.
[152] E. Angeles, et al., Computational studies of 1-hydrazinophthalazine (Hydralazine) as antineoplasic agent, Dock. Stud. Methyltransferase 2 (4) (2005) 282–286.
[153] X. Lin, et al., Reversal of GSTP1 CpG island hypermethylation and reactivation of π-class glutathione S-transferase (GSTP1) expression in human prostate cancer cells by treatment with procainamide, Cancer Res. 61 (24) (2001) 8611–8616.
[154] R.-K. Lin, C.-H. Hsu, Y.-C. Wang, Mithramycin a inhibits DNA methyltransferase and metastasis potential of lung cancer cells, Anti-Cancer Drugs 18 (10) (2007) 1157–1164.

[155] J. Huang, et al., RGS6 suppresses ras-induced cellular transformation by facilitating Tip60-mediated Dnmt1 degradation and promoting apoptosis, Oncogene 33 (27) (2014) 3604–3611.
[156] R.L. Fagan, et al., Laccaic acid a is a direct, DNA-competitive inhibitor of DNA methyltransferase 1, J. Biol. Chem. 288 (33) (2013) 23858–23867.
[157] A. Oodi, et al., Harmine, a novel DNA methyltransferase 1 inhibitor in the leukemia cell line, Indian J. Hematol. Blood Transfus. 33 (4) (2017) 509–515.
[158] W.J. Lee, B.T. Zhu, Inhibition of DNA methylation by caffeic acid and chlorogenic acid, two common catechol-containing coffee polyphenols, Carcinogenesis 27 (2) (2006) 269–277.
[159] C. Deng, et al., Hydralazine may induce autoimmunity by inhibiting extracellular signal–regulated kinase pathway signaling, Arthritis Rheum. 48 (3) (2003) 746–756.
[160] B. Segura-Pacheco, et al., Reactivation of tumor suppressor genes by the cardiovascular drugs hydralazine and procainamide and their potential use in cancer therapy, Clin. Cancer Res. 9 (5) (2003) 1596–1603.
[161] B. Segura-Pacheco, et al., Global DNA hypermethylation-associated cancer chemotherapy resistance and its reversion with the demethylating agent hydralazine, J. Transl. Med. 4 (1) (2006) 1–13.
[162] Y. Song, C. Zhang, Hydralazine inhibits human cervical cancer cell growth in vitro in association with APC demethylation and re-expression, Cancer Chemother. Pharmacol. 63 (4) (2009) 605–613.
[163] I. Graça, et al., Anti-neoplastic properties of hydralazine in prostate cancer, Oncotarget 5 (15) (2014) 5950.
[164] S. Jagadeesh, et al., Mahanine reverses an epigenetically silenced tumor suppressor gene RASSF1A in human prostate cancer cells, Biochem. Biophys. Res. Commun. 362 (1) (2007) 212–217.
[165] S. Agarwal, et al., Mahanine restores RASSF1A expression by down-regulating DNMT1 and DNMT3B in prostate cancer cells, Mol. Cancer 12 (1) (2013) 1–12.
[166] D. Kuck, et al., Nanaomycin a selectively inhibits DNMT3B and reactivates silenced tumor suppressor genes in human cancer cells, Mol. Cancer Ther. 9 (11) (2010) 3015–3023.
[167] C.J. Poole, et al., DNMT3B overexpression contributes to aberrant DNA methylation and MYC-driven tumor maintenance in T-ALL and Burkitt's lymphoma, Oncotarget 8 (44) (2017) 76898.
[168] O. Méndez-Lucio, et al., Toward drug repurposing in epigenetics: olsalazine as a hypomethylating compound active in a cellular context, ChemMedChem 9 (3) (2014) 560–565.
[169] H. Shin, Y.S. Lee, Y.C. Lee, Sodium butyrate-induced DAPK-mediated apoptosis in human gastric cancer cells, Oncol. Rep. 27 (4) (2012) 1111–1115.
[170] K.E. Joung, D.-K. Kim, Y.Y. Sheen, Antiproliferative effect of trichostatin a and HC-toxin in T47D human breast cancer cells, Arch. Pharm. Res. 27 (6) (2004) 640–645.
[171] M.R. Byun, et al., Repurposing natural products as novel HDAC inhibitors by comparative analysis of gene expression profiles, Phytomedicine 59 (2019), 152900.
[172] M. Pandey, et al., 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 (12) (2012) 952–962.
[173] K. Kumari, et al., Transcriptome analysis of genes associated with breast cancer cell motility in response to artemisinin treatment, BMC Cancer 17 (1) (2017) 1–13.
[174] M.M. Singh, et al., Inhibition of LSD1 sensitizes glioblastoma cells to histone deacetylase inhibitors, Neuro-Oncology 13 (8) (2011) 894–903.
[175] I.M. Bennani-Baiti, et al., Lysine-specific demethylase 1 (LSD1/KDM1A/AOF2/BHC110) is expressed and is an epigenetic drug target in chondrosarcoma, Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma, Hum. Pathol. 43 (8) (2012) 1300–1307.
[176] M. Wang, et al., Inhibition of LSD1 by pargyline inhibited process of EMT and delayed progression of prostate cancer in vivo, Biochem. Biophys. Res. Commun. 467 (2) (2015) 310–315.
[177] C. Sakane, et al., Inhibition of lysine-specific demethylase 1 by the acyclic diterpenoid geranylgeranoic acid and its derivatives, Biochem. Biophys. Res. Commun. 444 (1) (2014) 24–29.
[178] H. Han, et al., Synergistic re-activation of epigenetically silenced genes by combinatorial inhibition of DNMTs and LSD1 in cancer cells, PLoS One 8 (9) (2013), e75136.
[179] H. Jiang, et al., Discovery of novel BET inhibitors by drug repurposing of nitroxoline and its analogues, Org. Biomol. Chem. 15 (44) (2017) 9352–9361.
[180] J. Casaos, et al., Ribavirin as a potential therapeutic for atypical teratoid/rhabdoid tumors, Oncotarget 9 (8) (2018) 8054.
[181] K. Balasubramanyam, et al., Small molecule modulators of histone acetyltransferase p300, J. Biol. Chem. 278 (21) (2003) 19134–19140.
[182] B. Sung, et al., Anacardic acid (6-nonadecyl salicylic acid), an inhibitor of histone acetyltransferase, suppresses expression of nuclear factor-κB–regulated gene products involved in cell survival, proliferation, invasion, and inflammation through inhibition of the inhibitory subunit of nuclear factor-κBα kinase, leading to potentiation of apoptosis, Blood 111 (10) (2008) 4880–4891.
[183] A. Fudhaili, et al., Resveratrol epigenetically regulates the expression of zinc finger protein 36 in non-small cell lung cancer cell lines, Oncol. Rep. 41 (2) (2019) 1377–1386.
[184] B. Chatterjee, K. Ghosh, S.R. Kanade, Resveratrol modulates epigenetic regulators of promoter histone methylation and acetylation that restores BRCA1, p53, p21CIP1 in human breast cancer cell lines, Biofactors 45 (5) (2019) 818–829.
[185] C. Xu, et al., Chemical probes identify a role for histone deacetylase 3 in Friedreich's ataxia gene silencing, Chem. Biol. 16 (9) (2009) 980–989.
[186] Z. Liu, et al., Modulation of DNA methylation by a sesquiterpene lactone parthenolide, J. Pharmacol. Exp. Ther. 329 (2) (2009) 505–514.
[187] M.L. Hartman, et al., Parthenolide induces MITF-M downregulation and senescence in patient-derived MITF-mhigh melanoma cell populations, Oncotarget 7 (8) (2016) 9026.
[188] R.A.F. Gjaltema, M.G. Rots, Advances of epigenetic editing, Curr. Opin. Chem. Biol. 57 (2020) 75–81.
[189] A. Martinez-Escobar, B. Luna-Callejas, E. Ramón-Gallegos, CRISPR-dCas9-based artificial transcription factors to improve efficacy of cancer treatment with drug repurposing: proposal for future research, FrontiersOncology (2021) 3348.
[190] G. Velez, et al., Liquid biopsy proteomics of uveal melanoma reveals biomarkers associated with metastatic risk, Mol. Cancer 20 (1) (2021) 1–5.
[191] A. Bhardwaj, V. Nain, TALENs—an indispensable tool in the era of CRISPR: a mini review, J. Genetic Eng. Biotechnol. 19 (1) (2021) 1–10.
[192] F. Urnov, E. Rebar, M. Holmes, H.S. Zhang, P.D. Gregory, Nat. Rev. Genet 11 (2010) 636–646.
[193] J. Boch, et al., in: Breaking the Code of DNA Binding Specificity of TAL-type III Effectors 326, 2009, pp. 1509–1512, 5959.
[194] A.N.-S. Mak, et al., TAL effectors: function, structure, engineering and applications, Curr. Opin. Struct. Biol. 23 (1) (2013) 93–99.
[195] M.L. Maeder, et al., in: Targeted DNA demethylation and activation of endogenous genes using programmable TALE-TET1 fusion proteins 31, 2013, pp. 1137–1142, 12.
[196] E.M. Mendenhall, et al., in: Locus-specific Editing of Histone Modifications at Endogenous Enhancers 31, 2013, pp. 1133–1136, 12.
[197] A. Martella, D.I. Fisher, Regulation of gene expression and the elucidative role of CRISPR-based epigenetic modifiers and CRISPR-induced chromosome conformational changes, CRISPR J. 4 (1) (2021) 43–57.
[198] J.H. Goell, I.B. Hilton, CRISPR/Cas-based epigenome editing: advances, applications, and clinical utility, Trends Biotechnol. 39 (7) (2021) 678–691.
[199] L.A. Syding, et al., in: CRISPR/Cas9 Epigenome Editing Potential for Rare Imprinting Diseases: A Review 9, 2020, p. 993 (4).
[200] M. Adli, The CRISPR tool kit for genome editing and beyond, Nat Commun. 9 (2018) 1911. PUBMED.
[201] A. Majchrzak-Celińska, A. Warych, M.J.G. Szoszkiewicz, in: Novel Approaches to Epigenetic Therapies: From Drug Combinations to Epigenetic Editing 12, 2021, p. 208, 2.
[202] B. Schmeck, et al., Intracellular bacteria differentially regulated endothelial cytokine release by MAPK-dependent histone modification, J. Immunol. 175 (5) (2005) 2843–2850.
[203] P.I. Thakore, et al., in: Highly Specific Epigenome Editing by CRISPR-Cas9 Repressors for Silencing of Distal Regulatory Elements 12, 2015, pp. 1143–1149, 12.
[204] M. Esteller, Epigenetics in cancer, N. Engl. J. Med. 358 (11) (2008) 1148–1159.
[205] S. Shukla, S.M. Meeran, S.K. Katiyar, Epigenetic regulation by selected dietary phytochemicals in cancer chemoprevention, Cancer Lett. 355 (1) (2014) 9–17.
[206] L.T. Kagohara, et al., Epigenetic regulation of gene expression in cancer: techniques, resources and analysis, Brief. Funct. Genomics 17 (1) (2018) 49–63.
[207] M. Zadi Heydarabad, et al., Regulatory effect of resveratrol and prednisolone on MDR1 gene expression in acute lymphoblastic leukemia cell line (CCRF-CEM): an epigenetic perspective, J. Cell. Biochem. 119 (6) (2018) 4890–4896.
[208] W.-T. Yang, P.-S. Zheng, Promoter hypermethylation of KLF4 inactivates its tumor suppressor function in cervical carcinogenesis, PloS one 9 (2) (2014), e88827.
[209] Y. Zhou, Bin, et al., Natural polyphenols for prevention and treatment of cancer, Nutrients 8 (8) (2016) 515.
[210] M.W. Luczak, P.P. Jagodziński, The role of DNA methylation in cancer development, Folia Histochem. Cytobiol. 44 (3) (2006) 143–154.
[211] Á. Carlos-Reyes, et al., Dietary compounds as epigenetic modulating agents in cancer, Front. Genet. 10 (2019) 79.
[212] V.S. Thakur, et al., Plant phytochemicals as epigenetic modulators: role in cancer chemoprevention, AAPS J. 16 (1) (2014) 151–163.
[213] T.M. Hardy, T.O.J.E. Tollefsbol, in: Epigenetic Diet: Impact on the Epigenome and Cancer 3, 2011, pp. 503–518, 4.
[214] V. Aggarwal, et al., in: Garcinol Exhibits Anti-neoplastic Effects by Targeting Diverse Oncogenic Factors in Tumor Cells 8, 2020, p. 103, 5.
[215] S.J. Hewlings, D.S.J.F. Kalman, in: Curcumin: A Review of Its Effects on Human Health 6, 2017, p. 92, 10.
[216] I. Nardi, et al., Triptolide inhibits wnt signaling in NSCLC through upregulation of multiple wnt inhibitory factors via epigenetic modifications to histone H3, Int. J. Cancer 143 (10) (2018) 2470–2478.
[217] S. Hang, X. Wang, H. Li, Triptolide inhibits viability and migration while promotes apoptosis in nephroblastoma cells by regulation of miR-193b-3p, Exp. Mol. Pathol. 108 (2019) 80–88.
[218] M. Alhosin, Thymoquinone is a novel potential inhibitor of SIRT1 in cancers with p53 mutation: role in the reactivation of tumor suppressor p73, World Acad. Sci. J. 2 (4) (2020) 1.
[219] M.A. Khan, M. Tania, J. Fu, Epigenetic role of thymoquinone: impact on cellular mechanism and cancer therapeutics, Drug Discov. Today 24 (12) (2019) 2315–2322.
[220] M. Mitsiogianni, et al., Sulforaphane and iberin are potent epigenetic modulators of histone acetylation and methylation in malignant melanoma, Eur. J. Nutr. 60 (1) (2021).
[221] S. Khan, et al., MicroRNA-10a is reduced in breast cancer and regulated in part through retinoic acid, BMC Cancer 15 (1) (2015) 1–8.
[222] L. Wang, A.P. Rohatgi, Y.-J.Y. Wan, Retinoic acid and microRNA, Methods Enzymol. 637 (2020) 283–308.

[223] S. Venturelli, et al., Resveratrol as a pan-HDAC inhibitor alters the acetylation status of jistone proteins in human-derived hepatoblastoma cells, PLoS One 8 (8) (2013), e73097.
[224] D. Cao, et al., Structural basis for allosteric, substrate-dependent stimulation of SIRT1 activity by resveratrol, Genes Dev. 29 (12) (2015) 1316–1325.
[225] W. Qin, et al., Methylation and miRNA effects of resveratrol on mammary tumors vs. Normal tissue, Nutr. Cancer 66 (2) (2014) 270–277.
[226] J. Zhao, et al., Quercetin inhibits cell viability, migration and invasion by regulating miR-16/HOXA10 axis in oral cancer, Eur. J. Pharmacol. 847 (2019) 11–18.
[227] X. Zhang, et al., Quercetin enhances cisplatin sensitivity of human osteosarcoma cells by modulating microRNA-217-KRAS axis, Molecules and cells 38 (7) (2015) 638.
[228] M. Zheng, Y. Wu, Piceatannol suppresses proliferation and induces apoptosis by regulation of the microRNA-21/phosphatase and tensin homolog/protein kinase B signaling pathway in osteosarcoma cells, Mol. Med. Rep. 22 (5) (2020) 3985–3993.
[229] C. Zhang, et al., Phenethyl isothiocyanate (PEITC) suppresses prostate cancer cell invasion epigenetically through regulating microRNA-194, Mol. Nutr. Food Res. 60 (6) (2016) 1427–1436.
[230] T. Zhang, et al., MiR-135a and MRP1 play pivotal roles in the selective lethality of phenethyl isothiocyanate to malignant glioma cells, Am. J. Cancer Res. 6 (5) (2016) 957.
[231] M. Dawood, E. Ooko, T. Efferth, Collateral sensitivity of parthenolide via NF-κB and HIF-α inhibition and epigenetic changes in drug-resistant cancer cell lines, Front. Pharmacol. 10 (2019) 542.
[232] H. Nian, et al., Modulation of histone deacetylase activity by dietary isothiocyanates and allyl sulfides: studies with sulforaphane and garlic organosulfur compounds, Environ. Mol. Mutagen. 50 (3) (2009) 213–221.
[233] N. Druesne-Pecollo, P. Latino-Martel, Modulation of histone acetylation by garlic sulfur compounds, Anti Cancer Agents Med. Chem. 11 (3) (2011) 254–259.
[234] F. Shuai, et al., Effects of gossypol acetic acid on the proliferation and methylation level of the human MutL homologue 1 gene in human tongue carcinoma cell line Tca8113, West China J. Stomatol. 32 (1) (2014).
[235] A. King-Batoon, J.M. Leszczynska, C.B. Klein, Modulation of gene methylation by genistein or lycopene in breast cancer cells, Environ. Mol. Mutagen. 49 (1) (2008) 36–45.
[236] A. Berger, et al., Kaempferol, a new nutrition-derived pan-inhibitor of human histone deacetylases, J. Nutr. Biochem. 24 (6) (2013) 977–985.
[237] F. Nouriemamzaden, et al., Modulation of estrogen α and progesterone receptors in triple negative breast cancer cell lines: the effects of vorinostat and indole-3-carbinol in vitro, Anticancer Res. 40 (7) (2020) 3669–3683.
[238] K.G. Hargraves, L. He, G.L. Firestone, Phytochemical regulation of the tumor suppressive microRNA, miR-34a, by p53-dependent and independent responses in human breast cancer cells, Mol. Carcinog. 55 (5) (2016) 486–498.
[239] Y. Gui, et al., Icariin, a flavonoid with anti-cancer effects, alleviated paclitaxel-induced neuropathic pain in a SIRT1-dependent manner, Mol. Pain 14 (2018), 1744806918768970.
[240] J. Tang, et al., Gossypol acetate induced apoptosis of pituitary tumor cells by targeting the BCL-2 via the upregulated microRNA miR-15a, Int. J. Clin. Exp. Med. 8 (6) (2015) 9079.
[241] L.D. Godoy, et al., Targeting the epigenome: screening bioactive compounds that regulate histone deacetylase activity, Mol. Nutr. Food Res. 61 (4) (2017) 1600744.
[242] M.K. Sundaram, et al., Genistein modulates signaling pathways and targets several epigenetic markers in HeLa cells, Genes 10 (12) (2019) 955.
[243] M. Farhan, et al., Garcinol sensitizes NSCLC cells to standard therapies by regulating EMT-modulating miRNAs, Int. J. Mol. Sci. 20 (4) (2019) 800.
[244] V. Aggarwal, et al., Molecular mechanisms of action of epigallocatechin gallate in cancer: recent trends and advancement, in: Seminars in Cancer Biology, Elsevier, 2020.
[245] M.A. Khan, et al., (-)-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 (4) (2015) 1976–1984.
[246] Y. Zhu, et al., Epigallocatechin gallate inhibits cell growth and regulates miRNA expression in cervical carcinoma cell lines infected with different high-risk human papillomavirus subtypes, Exp. Therapeutic Med. 17 (3) (2019) 1742–1748.
[247] S.S. Soflaei, et al., Curcumin: a natural pan-HDAC inhibitor in cancer, Curr. Pharm. Des. 24 (2) (2018) 123–129.
[248] M. Gallardo, et al., Curcumin rescues breast cells from epithelial-mesenchymal transition and invasion induced by anti-miR-34a, Int. J. Oncol. 56 (2) (2020) 480–493.
[249] M. Sikander, et al., Cucurbitacin D exhibits potent anti-cancer activity in cervical cancer, Sci. Rep. 6 (1) (2016) 1–13.
[250] S. Shukla, et al., Cucurbitacin B alters the expression of tumor-related genes by epigenetic modifications in NSCLC and inhibits NNK-induced lung tumorigenesis, Cancer Prev. Res. 8 (6) (2015) 552–562.
[251] H. Liu, et al., Effect of evodiamine and berberine on miR-429 as an oncogene in human colorectal cancer, OncoTargets Ther. 9 (2016) 4121.
[252] C. Huang, et al., Effect of evodiamine and berberine on the interaction between DNMTs and target microRNAs during malignant transformation of the colon by TGF-β1, Oncol. Rep. 37 (3) (2017) 1637–1645.
[253] H.-Y. You, et al., Berberine modulates cisplatin sensitivity of human gastric cancer cells by upregulation of miR-203, In Vitro Cellular & Developmental Biology-Animal 52 (8) (2016) 857–863.
[254] A.E. Wagner, et al., Anti-inflammatory potential of allyl-isothiocyanate–role of Nrf2, NF-κB and microRNA-155, J. Cell. Mol. Med. 16 (4) (2012) 836–843.
[255] R. Feil, M.F. Fraga, Epigenetics and the environment: emerging patterns and implications, Nat. Rev. Genet. 13 (2) (2012) 97–109.
[256] C.A. Thaiss, et al. (6), in: Microbiota Diurnal Rhythmicity Programs Host Transcriptome Oscillations 167, 2016, pp. 1495–1510. e12.
[257] Y. Wang, et al., in: The Intestinal Microbiota Regulates Body Composition Through NFIL3 and the Circadian Clock 357, 2017, pp. 912–916, 6354.
[258] L. Cervantes-Barragan, et al., in: Lactobacillus reuteri Induces Gut Intraepithelial CD4+ CD8αα+ T Cells 357, 2017, pp. 806–810, 6353.
[259] M.X. Byndloss, et al., in: Microbiota-activated PPAR-γ Signaling Inhibits Dysbiotic Enterobacteriaceae Expansion 357, 2017, pp. 570–575, 6351.
[260] S. Magnúsdóttir, et al., in: Systematic Genome Assessment of B-vitamin Biosynthesis Suggests Co-operation Among Gut Microbes 6, 2015, p. 148.
[261] M.S. Diamond, M. Farzan, The broad-spectrum antiviral functions of IFIT and IFITM proteins, Nat. Rev. Immunol. 13 (1) (2013) 46–57.
[262] R. Kellermayer, et al., in: Colonic Mucosal DNA Methylation, Immune Response, and Microbiome Patterns in Toll-like Receptor 2-Knockout Mice 25, 2011, pp. 1449–1460, 5.
[263] P. D'Aquila, et al., in: Gut Microbiota as Important Mediator Between Diet and DNA Methylation and Histone Modifications in the Host 12, 2020, p. 597, 3.
[264] H.M. Hamer, et al., in: The Role of Butyrate on Colonic Function 27, 2008, pp. 104–119, 2.
[265] S. Hu, et al., in: The Microbe-derived Short Chain Fatty Acid Butyrate Targets miRNA-dependent p21 Gene Expression in Human Colon Cancer 6, 2011, p. e16221 (1).
[266] Y. Li, et al., in: Role of the miR-106b-25 microRNA cluster in hepatocellular carcinoma 100, 2009, pp. 1234–1242, 7.
[267] Y. Xie, et al., in: MicroRNA-24 Regulates XIAP to Reduce the Apoptosis Threshold in Cancer Cells 32, 2013, pp. 2442–2451, 19.
[268] Y. Qin, P.A. Wade, Crosstalk between the microbiome and epigenome: messages from bugs, J. Biochem. 163 (2) (2018) 105–112.
[269] G. Den Besten, et al., in: The Role of Short-chain Fatty Acids in the Interplay Between Diet, Gut Microbiota, and Host Energy Metabolism 54, 2013, pp. 2325–2340 (9).
[270] C. Gerhauser, Impact of dietary gut microbial metabolites on the epigenome, Philos. Trans. R. Soc. B Biol Sci. 373 (1748) (2018) 20170359.
[271] H.J. Flint, et al., in: Polysaccharide Utilization by Gut Bacteria: Potential for New Insights From Genomic Analysis 6, 2008, pp. 121–131, 2.
[272] S.N. Zucker, et al., Nrf2 amplifies oxidative stress via induction of Klf9, Mol. Cell 53 (6) (2014) 916–928.
[273] M.G. Rooks, W.S. Garrett, Gut microbiota, metabolites and host immunity, Nat. Rev. Immunol. 16 (6) (2016) 341–352.
[274] L. Lin, J.J.B.i. Zhang, in: Role of Intestinal Microbiota and Metabolites on Gut Homeostasis and Human Diseases 18, 2017, pp. 1–25 (1).
[275] N. Reichardt, et al., in: Phylogenetic Distribution of Three Pathways for Propionate Production Within the Human Gut Microbiota 8, 2014, pp. 1323–1335, 6.
[276] D. Ríos-Covián, et al., in: Intestinal Short Chain Fatty Acids and Their Link With Diet and Human Health 7, 2016, p. 185.
[277] P. Louis, et al., in: Diversity of human colonic butyrate-producing bacteria revealed by analysis of the butyryl-CoA: acetate CoA-transferase gene 12, 2010, pp. 304–314, 2.
[278] D. Sun, Y. Chen, J.-Y.J.N.S.R. Fang, Influence of the microbiota on epigenetics in Colorectal Cancer, Natl. Sci. Rev. 6 (6) (2019) 1138–1148.
[279] M. Bots, R.W. Johnstone, Rational combinations using HDAC inhibitors, Clin. Cancer Res. 15 (12) (2009) 3970–3977.
[280] J.R. Davie, Inhibition of histone deacetylase activity by butyrate, J. Nutr. 133 (7) (2003) 2485S–2493S.
[281] S. Jabs, et al., Impact of the gut microbiota on the m 6 a epitranscriptome of mouse cecum and liver, Nat. Commun. 11 (1) (2020) 1–16.
[282] M. Remely, et al., Effects of short chain fatty acid producing bacteria on epigenetic regulation of FFAR3 in type 2 diabetes and obesity, Gene 537 (1) (2014) 85–92.
[283] Y. Wu, et al., Dissecting the interplay mechanism between epigenetics and gut microbiota: health maintenance and disease prevention, Int. J. Mol. Sci. 22 (13) (2021) 6933.
[284] S. Hu, et al., Butyrate inhibits pro-proliferative miR-92a by diminishing c-myc-induced miR-17-92a cluster transcription in human colon cancer cells, Mol. Cancer 14 (1) (2015) 1–15.
[285] J. Schulthess, et al., The short chain fatty acid butyrate imprints an antimicrobial program in macrophages, Immunity 50 (2) (2019) 432–445, e7.
[286] J. Whitt, et al., Disruption of epithelial HDAC3 in intestine prevents diet-induced obesity in mice, Gastroenterology 155 (2) (2018) 501–513.
[287] H.N. Sanchez, et al., B cell-intrinsic epigenetic modulation of antibody responses by dietary fiber-derived short-chain fatty acids, Nat. Commun. 11 (1) (2020) 1–19.
[288] J. Paluszczak, V. Krajka-Kuźniak, W. Baer-Dubowska, The effect of dietary polyphenols on the epigenetic regulation of gene expression in MCF7 breast cancer cells, Toxicol. Lett. 192 (2) (2010) 119–125.
[289] M. Remely, et al., EGCG prevents high fat diet-induced changes in gut microbiota, decreases of DNA strand breaks, and changes in expression and DNA methylation of Dnmt1 and MLH1 in C57BL/6J male mice, Oxidative Med. Cell. Longev. 2017 (2017).

[290] K. Nakata, et al., Commensal microbiota-induced microRNA modulates intestinal epithelial permeability through the small GTPase ARF4, J. Biol. Chem. 292 (37) (2017) 15426–15433.
[291] R. Daillère, et al., Enterococcus hirae and barnesiella intestinihominis facilitate cyclophosphamide-induced therapeutic immunomodulatory effects, Immunity 45 (4) (2016) 931–943.
[292] Z. Kuang, et al., The intestinal microbiota programs diurnal rhythms in host metabolism through histone deacetylase 3, Science 365 (6460) (2019) 1428–1434.
[293] X. Xue, et al., Downregulation of micro RNA-107 in intestinal CD 11c+ myeloid cells in response to microbiota and proinflammatory cytokines increases IL-23p19 expression, Eur. J. Immunol. 44 (3) (2014) 673–682.
[294] D.-H. Yu, et al., Postnatal epigenetic regulation of intestinal stem cells requires DNA methylation and is guided by the microbiome, Genome Biol. 16 (1) (2015) 1–16.
[295] S.-E. Wu, et al., Microbiota-derived metabolite promotes HDAC3 activity in the gut, Nature 586 (7827) (2020) 108–112.
[296] G. Wieërs, et al., How probiotics affect the microbiota, Front. Cell. Infect. Microbiol. 9 (2020) 454.
[297] K. Takahashi, et al., Epigenetic control of the host gene by commensal bacteria in large intestinal epithelial cells, J. Biol. Chem. 286 (41) (2011) 35755–35762.
[298] A. Pacis, et al., Bacterial infection remodels the DNA methylation landscape of human dendritic cells, Genome Res. 25 (12) (2015) 1801–1811.
[299] L. Zheng, et al., Microbial-derived butyrate promotes epithelial barrier function through IL-10 receptor–dependent repression of claudin-2, J. Immunol. 199 (8) (2017) 2976–2984.
[300] P. Pan, et al., L Oss of FFAR 2 promotes colon cancer by epigenetic dysregulation of inflammation suppressors, Int. J. Cancer 143 (4) (2018) 886–896.
[301] D.E. Kok, W.T. Steegenga, J.A. McKay, Folate and epigenetics: why we should not forget bacterial biosynthesis, Future Medicine. (2018) 1147–1150.
[302] M. Rossi, A. Amaretti, S. Raimondi, Folate production by probiotic bacteria, Nutrients 3 (1) (2011) 118–134.
[303] J.-H. Son, H. Cheon, Toward cancer treatment using terahertz radiation: demethylation of cancer cells, in: Next-generation Spectroscopic Technologies XIII, International Society for Optics and Photonics, 2020.
[304] H. Cheon, et al., Detection and manipulation of methylation in blood cancer DNA using terahertz radiation, Sci. Rep. 9 (1) (2019) 1–10.
[305] D.S. Sitnikov, et al., Effects of high intensity non-ionizing terahertz radiation on human skin fibroblasts, Biomed. Opt. Express 12 (11) (2021) 7122–7138.
[306] V. Fedorov, et al., The influence of terahertz radiation on the cell's genetic apparatus, J. Opt. Technol. 84 (8) (2017) 509–514.
[307] H. Cheon, J.-H. Son, Terahertz molecular resonance of cancer DNA, in: 42nd International Conference on Infrared, Millimeter, and Terahertz Waves (IRMMW-THz), IEEE, 2017.
[308] T.O. Khor, et al., Epigenetic DNA methylation of antioxidative stress regulator NRF2 in human prostate cancer, Cancer Prev. Res. 7 (12) (2014) 1186–1197.
[309] A. Bernd, Visible light and/or UVA offer a strong amplification of the anti-tumor effect of curcumin, Phytochem. Rev. 13 (1) (2014) 183–189.
[310] S. Kalghatgi, et al., Effects of non-thermal plasma on mammalian cells, PLoS One 6 (1) (2011), e16270.
[311] M. Keidar, et al., Cold plasma selectivity and the possibility of a paradigm shift in cancer therapy, Br. J. Cancer 105 (9) (2011) 1295–1301.
[312] S.J. Kim, T. Chung, Cold atmospheric plasma jet-generated RONS and their selective effects on normal and carcinoma cells, Sci. Rep. 6 (1) (2016) 1–14.
[313] P. Morales-Ramirez, et al., Assessing cellular DNA damage from a helium plasma needle, Radiat. Res. 179 (6) (2013) 669–673.
[314] S. Lee, et al., Epigenetic silencing of miR-19a-3p by cold atmospheric plasma contributes to proliferation inhibition of the MCF-7 breast cancer cell, Sci. Rep. 6 (1) (2016) 1–10.
[315] Z. Liu, Y. Gao, X. Li, Cancer epigenetics and the potential of epigenetic drugs for treating solid tumors, Expert. Rev. Anticancer. Ther. 19 (2) (2019) 139–149.
[316] F. Chen, et al., Nanoparticle-based drug delivery systems for targeted epigenetics cancer therapy, Curr. Drug Targets 21 (11) (2020) 1084–1098.
[317] S.-Y. Li, et al., Combination therapy with epigenetic-targeted and chemotherapeutic drugs delivered by nanoparticles to enhance the chemotherapy response and overcome resistance by breast cancer stem cells, J. Control. Release 205 (2015) 7–14.
[318] S.Y. Wu, et al., RNAi therapies: drugging the undruggable, Sci. Transl. Med. 6 (240) (2014), 240ps7.
[319] M.R. Gedda, et al., Epigenetic aspects of engineered nanomaterials: is the collateral damage inevitable? Front.Bioeng. Biotechnol. (2019) 228.