Role of histone deacetylases in blood cancer: Exploring peptide-based inhibitors as therapeutic strategies for leukemia treatment (Review)

YANEENART SUWANWONG[1] and PHORNTHIP PLOENSIL[2]

[1]Department of Clinical Microscopy, Faculty of Allied Health Sciences, Chulalongkorn University, Bangkok 10330, Thailand; [2]Faculty of Medical Technology, Rangsit University, Pathumthani 12000, Thailand

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Abstract. Leukemia is a group of hematologic malignancies characterized by the uncontrolled proliferation of abnormal white blood cells, posing significant challenges for diagnosis and treatment because of its complex etiology. Both genetic and environmental factors contribute to leukemogenesis, with recent research highlighting the critical role of epigenetic modifications, particularly histone acetylation and deacetylation, in regulating gene expression and disease progression. Dysregulation of histone deacetylases (HDACs) is frequently observed in leukemia and is correlated with poor prognosis and resistance to conventional therapies. This observation has led to the development of epigenetic drugs for leukemia treatment. The emergence of HDAC inhibitors (HDACis) as targeted therapeutics offers promising avenues for more selective and effective leukemia treatments. The present review covers basic aspects of histone modification and its role in leukemogenesis and evaluates the potential of peptide-based HDACis as novel drugs for leukemia therapy.

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Correspondence to: Dr Yaneenart Suwanwong, Department of Clinical Microscopy, Faculty of Allied Health Sciences, Chulalongkorn University, 154 Payathai Road, Pathumwan, Bangkok 10330, Thailand
E-mail: yaneenart.s@chula.ac.th

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1. Introduction

Leukemia is a clonal malignant disorder of hematopoietic precursor cells that present as an excess of one or more hematologic cell types in the bone marrow and bloodstream. It is caused by a disruption of the normal processes of cell proliferation and cell death. There are four major types of leukemias: Acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML). The classification depends on the lineage and stage of the presenting leukemia cells and the rate of leukemia cell proliferation (1). In 2022, there were an estimated 48.7 hundred thousand new cases (ranked 13th of 33) and 30.5 hundred thousand deaths (ranked 10th of 33) from leukemia worldwide (2). Leukemia incidence varies among populations in different age groups and countries. ALL is most common in children and young adults, whereas AML, CLL and CML commonly occur in older adults. In adults aged ≥20 years, AML had the highest incidence and mortality rate among all leukemia types. A high incidence of leukemia has been reported in developed regions of the world such as Western Europe, North America and Australia (3,4). According to statistics acquired over the last three decades, in most regions, the cumulative risk of leukemia incidence has increased faster than the lifetime risk of leukemia mortality (5,6). The decreasing trends in mortality rates are potentially a result of significant advancements in leukemia diagnosis and therapies.

Conventionally, leukemia treatment relies on chemotherapy, which uses cytotoxic agents to destroy rapidly dividing leukemia cells. Principal chemotherapy drugs, including vincristine and an anthracycline, have been used in combination with other drugs, such as all-trans retinoic acid, cyclophosphamide, methotrexate and cytarabine, to achieve a satisfactory complete remission rate (7,8). However, since these drugs are not selective for cancer cells, they often cause undesirable side effects, some of which are more severe than others, such as neurotoxicity (9) and cardiomyopathy (10,11). These adverse effects not only worsen patient quality of life but also limit the dose and efficacy of chemotherapy drugs. Moreover, drug resistance and ineffectiveness in patients with some subtypes of leukemia have been reported (12,13).

Bone marrow or allogenic hematopoietic stem cell (HSC) transplantation can be options for the treatment of relapsed or refractory leukemia. Alternatively, novel therapeutic substances are needed to simultaneously overcome resistance and alleviate the adverse effects of chemotherapy. Over the past two decades, an improved understanding of the pathophysiology of leukemias has given rise to a rapid progress in leukemia therapeutic research. Targeted therapy began to play important roles in leukemia treatment. Cancer cell-selective drugs, including small molecule inhibitors targeting tyrosine kinases or phosphatidylinositol-3-kinases and antibodies against specific CD molecules, have emerged as attractive therapeutic options. To lower the dose of traditional cytotoxic drugs, such targeted drugs have often been applied in combination regimens. Cytogenetic and molecular aberrations are key factors that guide the development of targeted therapies. Consequently, they increase the complete cytogenetic response rate and improve patient quality of life in almost every type of leukemia (14). Excellent reviews discussing the advancement of leukemia therapy have been published recently (15,16). However, some leukemia subtypes are refractory or already resistant to newly developed drugs, making drug discovery research challenging.

Although genetic alterations of oncogenes play a significant role in leukemia progression, epigenetic aberrations have been shown to affect transcriptional regulation and the development of leukemia cells. In the past few years, several new therapeutic strategies have been proposed for the treatment of leukemia on the basis of epigenetic aberrations (17,18). Among numerous epigenetic modulators, histone deacetylase (HDAC), a deacetylase that acts on histone and non-histone proteins to alter chromatin structure and regulate gene expression, is the most intensively studied therapeutic target in leukemia (19). Overexpression of HDAC has been demonstrated to stimulate the progression of leukemogenesis and tumorigenesis by inhibiting tumor suppressor gene expression (20,21). Blocking HDAC activity reactivates tumor suppressor genes and directly suppresses tumor cell proliferation and induces apoptosis. This renders HDAC inhibitors (HDACis) potential targeted therapeutic agents for the management of leukemia and other cancers. Over the past decade, novel HDACis have been discovered and developed from both natural and synthetic sources (22,23). Among the various compounds that possess HDAC inhibition activity, peptides derived from diverse sources, including food, environment and laboratory production, are potential candidate HDACis that can influence epigenetic modulation (24). Compared with chemical drugs, peptide drugs provide advantages such as high specificity, low toxicity and biological diversity. Additionally, peptides can be rationally designed, which will be beneficial in targeted therapy development. The present review provides an overview of HDAC and HDACis types and functions with an emphasis on the role of HDACs in leukemogenesis. The development of HDACis and the HDAC inhibitory effects of potential therapeutic peptides on leukemia in preclinical and clinical trials are discussed.

2. HDACs and leukemia

HDAC classes and characteristics. Histone acetylation represents one of the main mechanisms of epigenetic modifications and is associated with two different enzymes, namely, histone acetyltransferases (HATs) and HDACs. HATs mediate the relaxation of nucleosomes to allow opening of chromatin by adding acetyl groups at the ε-amino group of N-terminal lysine residues in the histone tail, resulting in the upregulation of gene expression, whereas deacetylation mediated by HDACs removes acetyl groups and induces condensation of chromatin, resulting in the repression of the gene (25). An imbalance in the amount of HAT and HDAC enzymes interferes with the regulation of gene expression and induces the progression of several cancers (26).

In humans, HDACs include 18 enzymes categorized into two families: The classical HDAC family, which is composed of HDAC1-11, and the silent information regulator (SIR)-2 family, which is composed of SIRT1-7. These two families can be subdivided into four classes based on catalytic mechanisms and sequence homology to yeast deacetylases. HDACs in the same class possess similar structures and functions (27,28). HDAC class members and their characteristics are described in Table I.

Detailed information on the structure and catalytic mechanisms of each HDAC can be found in the extensive review by Asmamaw *et al* (29).

Roles of HDACs in hematopoiesis. All classes of HDACs participate in hematopoiesis by regulating multilineage blood cell development. Their functions involve stemness maintenance of HSCs and the lineage commitment of progenitor cells. HDACs interact with transcription factors and/or other cofactor proteins to modulate histone acetylation levels, which subsequently regulate the expression of several hematopoietic lineage-related genes (30-32). It has been shown that HDACs play crucial roles in the cell fate decisions of hematopoietic progenitors (33,34).

Class I HDACs, especially HDAC1, are major HDACs expressed in hematopoietic cells. They are found in all hematopoietic stages, but expression levels differ among the types of blood cells. HDAC1 is undetectable in early progenitor cells, moderately expressed in committed progenitor cells, and disappears in mature granulocytes, reflecting its dose-dependent role in modulating progenitor cell differentiation (35). A previous study in hematopoietic cell lines demonstrated that HDAC1 plays essential roles in maintaining the immature state of committed progenitor cells and contributes to GATA-1 mediated erythroid differentiation (36). HDAC1 transactivation is driven by Sp1 and GATA-1, whereas its transcriptional repression is mediated by C/EBPα and C/EBPβ (34). HDAC1 is accompanied by GATA1-Sp1 complexes during the differentiation of common myeloid progenitors (CMPs) into megakaryocyte-erythrocyte progenitor cells. By contrast, HDAC1 is downregulated by GATA2-C/EBP complexes during CMP differentiation into granulocyte-monocyte progenitor cells (37,38). The upregulation of HDAC1 facilitates the movement of granulocyte-monocyte progenitor cells toward granulocytic cells, whereas its downregulation induces the development of granulocyte-monocyte progenitor cells into monocytes, macrophages and dendritic cells (39). A previous study in a mouse model indicated that both HDAC1 and HDAC2 in a complex with their corepressor, Sin3A, serve as cell-autonomous regulators of HSC maintenance (40). They also play a role in the differentiation of megakaryocytic-erythroid

Table I. HDAC class members and their characteristics.

HDAC class	Members	Yeast deacetylase homologs	Cellular localization	Cofactor	Known functions
Class I	HDAC1, HDAC2, HDAC3, HDAC8	Rpd3	Predominant in nucleus	Zinc	Gene repression, chromatin condensation, cell cycle regulation
Class IIa	HDAC4, HDAC5, HDAC7, HDAC9	Hda1	Nucleus and cytoplasm	Zinc	Gene repression, cell differentiation, tissue development
Class IIb	HDAC6, HDAC10	Hda1	Predominant in cytoplasm	Zinc	Protein deacetylation (for example, tubulin), cell motility, stress response
Class III	SIRT1-7	Sir2 and Hst1	Nucleus (SIRT1, 6, and 7), cytoplasm (SIRT2) and mitochondria (SIRT3, 4, and 5)	NAD^+	Gene silencing, DNA repair, cellular stress response and metabolism, aging
Class IV	HDAC11	Hos1	Nucleus	Zinc	Gene repression, immune regulation

HDAC, histone deacetylase.

progenitor cells (41), pre-B cells (42), T lymphocytes (43) and NK cells (44). HDAC1 and HDAC3 are accompanied by Runx1 as repressor complexes to control the progression and maturation of granulocytes from progenitor cells, ensuring proper granulocytic development and function. Class IIa HDAC4 has been reported to act as a corepressor recruited by BCL6 to repress genes critical for regulating B-cell development process (45), and class IIa HDAC7 plays a role in the control of thymic selection during T-cell development (46). In addition, class IIb HDAC6 and class I HDAC2 stimulate the enucleation process of orthochromatic normoblasts. Members of class III HDACs have also been implicated in hematopoiesis. SIRT1 promotes the hematopoietic microenvironment through CXCL12 upregulation (47), and influences granulopoiesis through a regulatory loop between G-CFGR and G-CSF (48). Defects in hematopoietic progenitor differentiation and the downregulation of genes associated with hematopoietic development have been demonstrated in SIRT1-deficient mouse (49). SIRT2, SIRT3 and SIRT7 also play important roles in HSC maintenance and homeostasis, especially under stress and in elderly individuals (50-52). The last HDAC group, class IV HDAC11, is involved in the development of promyelocytes into neutrophils (53).

Implication of HDACs in leukemia. Abnormal histone deacetylation has been implicated in leukemia initiation and progression via two mechanisms; aberrant recruitment of an HDAC enzyme by an oncogenic fusion protein and alteration in the expression of HDACs. Some notable implications of HDACs in leukemogenesis are described.

It is well-known that one of the most common genetic rearrangements that causes leukemia is chromosome translocation, leading to the expression of fusion proteins associated with oncogenic transformation. In acute promyelocytic leukemia (APL), the most frequent chromosomal translocation t (15;17) results in the fusion protein PML-RARα. PML-induced dimerization of RARα enhances the binding of the corepressor complex NCoR/SMRT and class I and class II HDACs, thus repressing the expression of retinoic acid (RA)-target genes which in turn block differentiation of myeloid precursors (54). Similarly, other fusion proteins found in AML such as PLZF/RARα and AML1/EMO have been reported to induce transcriptional repression of genes critical to the differentiation of granulocytic precursors through enhanced recruitment of the HDAC-corepressor complex (55,56). HDAC1 and HDAC3 are recruited by fusion proteins such as AML1/ETO and subsequently form a complex that acts as an abnormal TF leading to leukemogenesis. Moreover, AML1-ETO can recruit HDAC1 and HDAC2 to bind NCoR-mSin3 and prevents leukemia cells from undergoing TNF-related apoptosis (57). Overexpression of SETBP1, an oncogenic protein resulting from t (12;18) in AML, was also reported to induce leukemia development through transcriptional repression of the critical hematopoiesis regulator gene Runx1 via recruitment of HDAC1 (58).

An imbalance in HAT and HDAC enzyme levels also affects gene transcription and is involved in the development of hematological malignancies. Cumulative evidence suggests that the aberrant hypoacetylation of histones associated with the overexpression of HDACs leads to the repression

of tumor suppressor genes that regulate the cell cycle and DNA repair pathways and alteration of the cell differentiation program, leading to leukemogenesis (59,35,60). The differential overexpression of HDAC isoforms is related to different subtypes of leukemia. For instance, HDAC1 overexpression is associated with ALL, CML and AML, whereas the high expression of HDAC3, 6, and 7 is linked to pathogenesis and prognosis in ALL and CLL (61). A comprehensive study of the expression of all 18 HDAC isoforms in 200 CLL patients by Van Damme *et al* (62) showed that there are variations in the expression levels of different HDACs. HDAC6, HDAC7, HDAC11, SIRT3, SIRT6 and SIRT7 were upregulated, whereas HDAC2 and SIRT4 were significantly downregulated in patients with CLL compared with normal B cells. Correlation analysis revealed that high levels of HDAC6 are significantly associated with longer treatment-free survival, and high levels of HDAC3, SIRT2, SIRT3 and SIRT6 are associated with a longer overall survival. Additionally, the results suggested that HDAC7 and HDAC10 overexpression and HDAC6 and SIRT3 under-expression are associated with poor prognosis (62). Recently, Verbeek *et al* (63) demonstrated that relevancy between Class IIA HDAC isoforms (HDAC4, HDAC5, HDAC7) shows critical prognostic relevance in KMT2A-rearranged ALL. Knockdown or selective inhibition of such HDAC isoforms induced apoptosis and impacted leukemic infiltration in protective niches such as bone marrow and CNS, which is crucial for prognosis in infant ALL (63). HDACs not only act on histone tails but also affect nonhistone substrates, including transcription factors and other cofactor proteins. The first described non-histone substrate of HATs and HDACS is the tumor suppressor p53 protein, which is the key transcription factor in cellular stress response pathways (64). P53 plays important roles in regulating several biological mechanisms, including cell proliferation, cell differentiation, the cell cycle, the apoptotic pathway and DNA repair (65). Normally, p53 activity is modulated by CBP/p300-mediated acetylation. It has been found that upregulation of HDAC1 potentially block apoptosis induced by the deacetylation of p53, which results in an increased survival rate of AML cells (66). In AML with inv(16)+, high expression of HDAC8 was detected in primitive CD34+ cells and it was recruited by CBFβ-SMMHC fusion proteins to form complexes with p53. These complexes mediate the aberrant deacetylation of p53 by HDAC8 and subsequently promote AML progression (67). Furthermore, high expression of class I HDACs induces aberrant acetylation of p53 and Ku70, resulting in resistance to imatinib in patients with CML with positive Philadelphia chromosome (68). It has been reported that HDAC7 regulates the phagocytic activity of monocyte-derived macrophages obtained from patients with CLL through direct modulation of BTK acetylation and phosphorylation. It has been suggested that HDAC7 contributes to therapeutic antibody resistance in patients with CLL and CLL who have high HDAC expression may result in a poor prognosis (69). The proven mechanisms that lead to abnormal deacetylation, resulting in leukemogenesis and leukemia progression, are depicted in Fig. 1.

Unlike genetic alterations, aberrant epigenetic modifications are reversible; therefore, targeting epigenetic modulators is a promising approach for the treatment of leukemia. Understanding of HDAC-related leukemogenesis has encouraged the development of HDACis that aim to restore normal gene expression by reactivating silenced tumor suppressor genes, inducing differentiation, and promoting the cessation of leukemia cell proliferation. In recent years, numerous HDACis have been extensively investigated in the search for viable therapeutics for leukemia. Some HDACis can be combined with conventional therapy to improve treatment efficacy and overcome resistance. Moreover, precision therapy can be established by rationally designing selective HDACi-based treatments via the guidance of HDAC expression profiling or the development of muti-targeted dual/hybrid inhibitors.

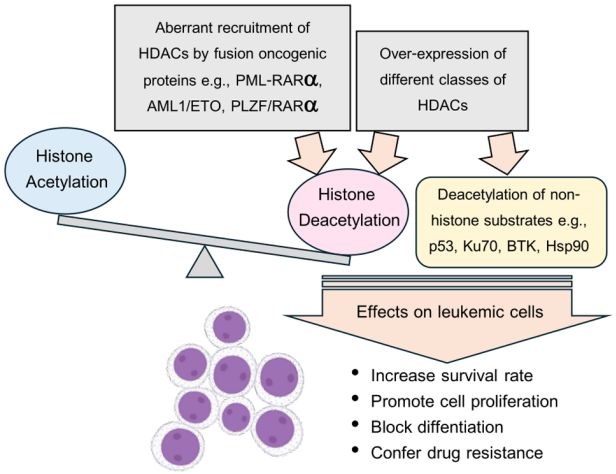

Figure 1. Mechanisms leading to imbalance of HAT and HDAC function, which results in leukemia progression. HDAC, histone deacetylase.

3. HDACis

As aforementioned, several lines of evidence suggest that the aberrant expression and function of HDAC enzymes play important roles in several solid cancers and hematological malignancies. HDACs facilitate tumor suppressor gene silencing in cancer cells, preventing them from undergoing apoptosis. Thus, the development of a new therapeutic agent that targets the HDAC enzyme to restore the acetylation of histones is needed (Fig. 2). It has been clearly described that HDACis can induce cell cycle arrest and cancer cell death. The main inhibitory mechanism of HDACis involves blocking the substrate binding of HDAC by interacting with the enzyme catalytic domain. HDACis have been discovered and identified from both natural and synthetic sources. HDACis can be classified into 4 groups based on their chemical structure. The three groups are small-molecule inhibitors, which include short-chain fatty acids, hydroxamic acids and benzamides. The other group is cyclic peptide inhibitors. Small-molecule HDACis are usually pan-HDACis, whereas peptide-based HDACis are more class-selective or isoform-selective HDACis due to their larger molecular dimensions and conformational flexibility. This feature enables them to mimic natural protein interactions more precisely. All HDACis share the same core structure consisting of three domains, which consists of a cap region, a hydrophobic linker and a zinc binding group (ZBG). The cap region interacts on

Table II. Summary of differences between small molecules and peptide-based HDAC inhibitors.

Characteristics	Types of HDAC inhibitors	
	Small molecule	Peptide
Size	Small (M.W. 100-500 Da)	Large (M.W. 400-1,500 Da)
IC_{50} values against leukemia cell line	Sub-micromolar to micromolar levels	Nanomolar level
Selectivity toward HDAC isoforms	Low	High
Toxicity and adverse Effect	High	Low
Clinical status	Advances in clinical development	Most are in preclinical or early-stage research phases
	Some are FDA approved	Only one is US FDA approved (romidepsin)

HDAC, histone deacetylase; M.W., molecular weight.

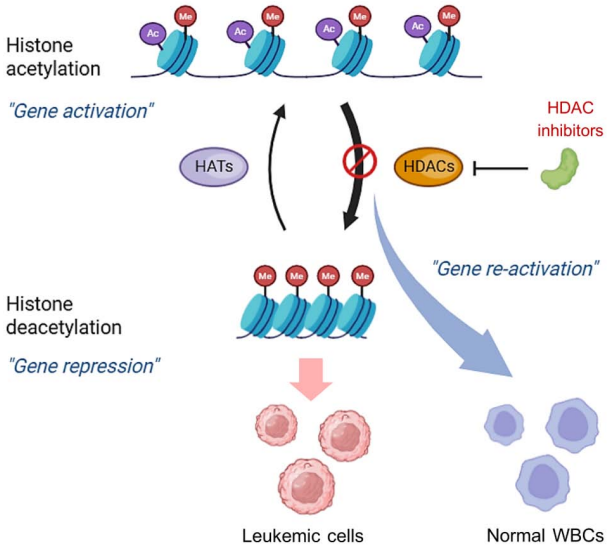

Figure 2. Function of HDACis to transform leukemic cells into normal WBCs. HDACs promote tumor suppressor gene silencing in leukemic cells. The major inhibitory mechanism of HDACis is to disrupt HDAC substrate binding, hence restoring histone acetylation and reactivating tumor suppressor genes. HDAC, histone deacetylase; HDACis, HDAC inhibitors; WBCs, white blood cells; HATs, histone acetyltransferases.

the surface at the entrance of the substrate, ZBG is the position of the functional group that binds and chelates a zinc ion in the catalytic site, and the hydrophobic linker domain is the region between the cap region and ZBG (70,71). Peptide inhibitors typically have a more complex 'cap group' that binds extensively to the enzyme surface (72), triggering disruption of HDAC interactions with specific corepressor complexes or chromatin-associated scaffolds in leukemia cells. This allows them to potentially modulate leukemia-specific epigenetic states more precisely. On the other hand, small-molecule inhibitors predominantly rely on zinc-chelation and catalytic site blockade, thus broadly inhibiting catalytic activity and affecting multiple HDAC isoforms and complexes (73). This mechanistic difference highlights the potential of peptides for refined epigenetic therapy in leukemia. The differences between small-molecule and peptide-based HDACis are summarized in Table II.

Short-chain fatty acids. Short-chain fatty acids such as butyrate and valproic acid (VPA) are inhibitors of class I and IIa HDACs. Butyrate is produced natively by anaerobic bacterial fermentation of carbohydrates in the colon and longer-chain fatty acid metabolism. It has been reported that the possible HDAC inhibition mechanism of butyrate may be attributed to its hydrophobic interaction with the HDAC active pocket; hence, it binds non-specifically (74). Butyrate induces the hyperacetylation of histones, regulating gene expression, and has been used for cancer treatment (75,76). It is characterized by low activity, short half-life and rapid metabolism, leading to a high effective concentration *in vivo* (77,78). VPA, a short chain aliphatic acid, has been reported to have antileukemic effects, such as anti-proliferation, induction of differentiation and stimulation of apoptosis, in AML (79,80). Certain studies have shown that VPA also has low HDAC inhibition activity; however, the combination of VPA with another chemotherapy drugs could increase the response in patients with leukemia (81,82).

Hydroxamic acids. Hydroxamic acids are organic compounds that can form table complexes with a variety of metal ions; therefore, their mechanism of action involves chelation zinc ions in the HDAC catalytic site (71). Hydroxamic acids act as potent pan-HDACis that affect HDAC classes I and II. Trichostatin A (TSA) is a naturally occurring compound that consists of an aromatic group as a cap region linked by a diene region connected to the hydroxamate tail. TSA has been proposed as an effective drug for the treatment of CLL (83). Since it has been shown that the mutant HDAC enzyme affects the binding activity between TSA and HDAC isoforms, TSA is used in clinical treatment with limitations (84). Suberoylanilide hydroxamic acid (SAHA; vorinostat) is a synthetic hydroxamic acid-containing HDACi that is structurally related to TSA. SAHA was approved by the FDA for the treatment of refractory cutaneous T-cell lymphoma (85). Other HDACi drugs composed of hydroxamic acid groups are belinostat and panobinostat (86,87). These hydroxamate compounds have been recently investigated in clinical trials for the treatment of other hematological malignancies.

Benzamides. Benzamides (amino anilides) are synthetic compounds that display selective inhibitory activity against

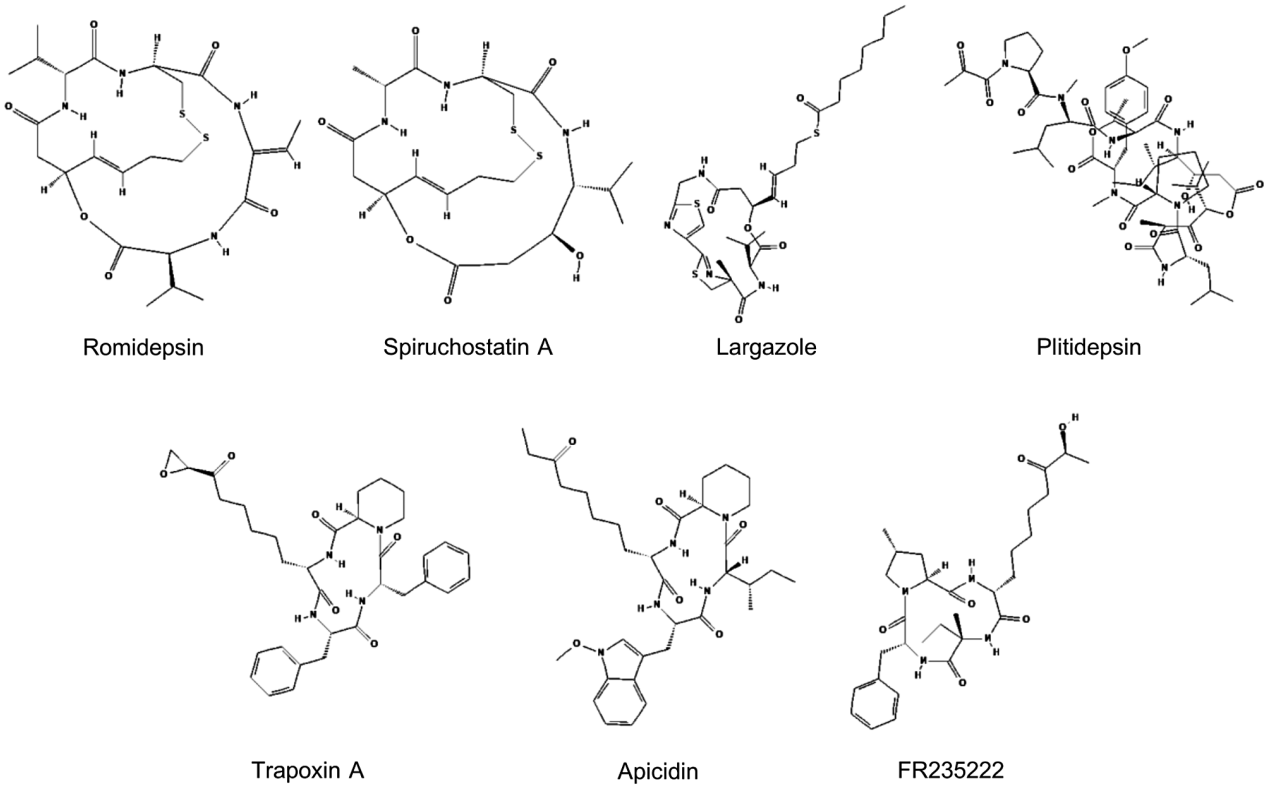

Figure 3. Chemical structures of 7 cyclic peptide HDAC inhibitors that have been investigated as anti-leukemic agents. Chemical structures were created using https://pubchem.ncbi.nlm.nih.gov.

class I HDACs. Benzamides can interact with and chelate a zinc ion in the HDAC pocket site, but their chelating activity is lower than that of hydroxamate and cyclic peptide compounds (88). Several benzamide derivatives, including entinostat and mocetinostat, have been reported to inhibit malignant cell proliferation and are currently undergoing clinical trials for the treatment of hematologic malignancies (89,90).

Cyclic peptides. Cyclic peptides are the most structurally diverse class of HDACis. They can be divided into the following two main groups: Cyclic tetrapeptides and bicyclic depsipeptides. Cyclic tetrapeptides contain epoxy ketone groups that interact with amino acids at the HDAC catalytic site, mainly through covalent bonds. The bicyclic depsipeptide structure contains disulfide bonds that attach to a zinc ion in the HDAC active site, leading to inhibition of HDAC activity. These cyclic peptides play important roles in targeting different HDAC isoforms depending on variations in cap regions (72,91). Owing to their strong inhibitory activity and potential HDAC-isoform selectivity, cyclic peptides are being intensively studied as prospective candidates for anticancer therapy development. Insights into cyclic peptide HDACis that have been investigated for leukemia therapy applications are elaborated upon in the following section. Their chemical structures are shown in Fig. 3.

4. Peptide-based HDACis and their application in leukemia therapy

Romidepsin. Romidepsin (FK228), a natural bicyclic depsipeptide, was first isolated from the gram-negative bacterium, *Chromobacterium violaceum*, and characterized as an antitumor substance both *in vitro* and *in vivo* (92). Romidepsin possesses HDAC inhibitory activity by interacting with zinc ions in the active region of HDAC enzymes. It acts as a prodrug because it is reduced to the active compound after uptake into cells (93). Romidepsin is mainly responsible for binding class I HDAC enzymes, including HDAC1, HDAC2, HDAC3 and HDAC8, but this drug has minimal selectivity for HDAC6 targeting (94). It is the most extensively studied among peptide HDACis for its impact and mechanism of action in a hematological aspect. Since 2009, the FDA has approved romidepsin for the treatment of numerous hematological malignancies, including cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (95,96). Several lines of evidence demonstrate that romidepsin has antitumor effects in various subtypes of leukemia. Romidepsin demonstrated antileukemic activity against APL cell lines by inducing APL cell apoptosis via a mitochondria-dependent pathway and targeting the NF-κB and p53 transcription factors (97) and increasing cell differentiation induced by retinoic acid (98). With respect to CML, romidepsin has been associated with the induction of apoptosis by inactivation of the BCR-ABL fusion protein (99). Another study in AML1/ETO positive leukemia cell supported that romidepsin can exert both differentiation and cytotoxic activity in AML cells, regardless of the underlying genomic aberration (100). The combination of a DNA-methyltransferase inhibitor and romidepsin has been reported to enhance several biological activities, including histone hyperacetylation, cytotoxic activity and IL-3 expression, in leukemia cells (100,101). Additionally, the use of romidepsin in combination with

chemotherapy drugs has shown the potential to overcome drug resistance in numerous types of leukemia (102,103). Recently, a phase I trial of romidepsin in combination with gemcitabine, oxaliplatin, and dexamethasone (Romi-GemOxD), has been conducted in patients with relapsed or refractory aggressive lymphomas (104). The study showed that Romi-GemOxD is a well-tolerated and effective treatment option. The overall response rate was 52%, with a notably high complete response rate of 43%. Most toxicities were hematologic (thrombocytopenia and lymphopenia) which are manageable without delays in subsequent cycles.

Largazole. Largazole is a cyclic depsipeptide that contains a 4-methylthiazoline unit linearly fused with a thiazole ring. It is derived from marine cyanobacteria of *Symploca* spp (105). Largazole shares the same zinc-binding motif with romidepsin and spiruchostasin. It is also a prodrug that requires conversion to a thiol derivative in order to function. Largazole thiol has been shown to be a more effective HDACi than romidepsin and spiruchostasin (106). *In vitro*, largazole demonstrated significant suppressive activity in solid cancer cell lines (107). Several studies have synthesized analogs of largazole to improve its activity (108,109). To increase the stability of the peptide conformation and to enhance HDAC inhibitory activity, largazole was modified by addition of a C7-benzyl and the bithiazole analog and capping with an octanoyl group to generate largazole 4a. A study in the NB4 human leukemia cell line demonstrated that largazole 4a selectively inhibit the activity of class I and class II HDAC enzymes (HDAC1 and HDAC4, respectively). Additionally, it has been shown to upregulatep21 and R-tubulin acetylation at H3 in the NB4 cell line. However, this compound is less potent than SAHA (a pan HDAC inhibitor drug that the FDA approved for the treatment of relapsed CTCL). Previously, an *in vitro* study using leukemia cells harvested from patients with CML demonstrated that largazole induce apoptosis and inhibit CML cell proliferation (110). It was suggested that largazole exert its antileukemic effect by downregulating the expression of the RNA-binding protein Musashi-2, which subsequently suppresses the mammalian target of rapamycin signaling pathway.

Spiruchostatin. Spiruchostatins are natural products originally isolated from the bacterium *Pseudomonas* sp., and their structure and HDAC inhibitory function resemble those of romidepsin (111). Spiruchostatins are composed of 4 subtypes (spiruchostatin A, B, C and D), each with distinct chemical structures and biological activity (112). It has been demonstrated to exhibit potent antiproliferative effects on various types of cancer cells. Few studies have been conducted to investigate the effects of spiruchostatins on leukemia cells. Kanno *et al* (113) reported that spiruchostatin B (SP-B) has strong cytotoxic effects on several human leukemia cell lines. It was reported that SP-B induced apoptosis and cell cycle arrest in a leukemia cell line (NALM-6) mediated by HDAC inhibition and upregulation of the expression of the cell cycle regulatory protein $p21^{waf1/cip1}$ expression. Another study by Rehman *et al* (114) demonstrated that spiruchostatins A and B induce apoptosis in U937 lymphoma cell and this process is associated with the accumulation of reactive oxygen species.

Plitidepsin. Plitidepsin (Aplidin®), is a natural cyclic depsipeptide originally isolated from the Mediterranean tunicate *Aplidium albicans* and is an HDACi with a broad spectrum of anticancer effects (115). Mechanistically, it has been shown to induce cell cycle arrest in the G1 and G2 phases and apoptosis (116,117). Plitidepsin has been demonstrated to have minimal toxicity to normal bone marrow cells (118,119), encouraging its development for the treatment of several hematological malignancies including leukemia, lymphoma and multiple myeloma. It has been reported that plitidepsin selectively induces leukemia cell apoptosis via Fas/CD95 and triggering of the mitochondrial-mediated apoptotic signaling pathway (120). Several investigations have revealed that the induction of hematologic malignant cell apoptosis by plitidepsin involves the activation of the c-Jun N-terminal kinase (JNK) signaling pathway (121,122). In addition, the cytotoxic effect of plitidepsin on a lymphoblastic leukemia cell line (MOLT-4) appears to be caused by the inhibition of vascular endothelial growth factor (VEGF)/VEGF receptor-1 signaling (117,123). Studies in cells of patients with ALL and CLL have demonstrated that plitidepsin induces leukemia cell death in a dose- and time-dependent manner suggesting the potential antileukemic effects of plitidepsin (117,124). These results indicate that it might be useful and is worthy of further assessment in clinical trials. Owing to its limited antitumor activity but lack of cross-resistance to other cytotoxic drugs, plitidepsin has frequently been studied in combination with other drugs, which results in a higher response rate (124-126). A phase III clinical study of the use of plitidepsin in combination with dexamethasone in patients with relapsed/refractory multiple myeloma who had undergone 3 to 6 prior chemotherapies was conducted (127). The results showed a significant improvement in both the primary endpoint of progression-free survival and the overall survival. Lately, the phase I study of plitidepsin in combination with bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma has been reported (128). The result showed moderate overall response rate (22%) with acceptable safety profile with manageable hematologic toxicities. The favorable outcomes revealed by these two trials suggest that plitidepsin is beneficial for use as a salvage therapy.

Trapoxins. Trapoxins are cyclic tetrapeptides isolated from cultured broth of the fungus *Helicoma ambiens*. Two trapoxin derivatives, trapoxin A and trapoxin B, have been identified. Their chemical structures consist of an uncommon amino acid Aoe (2-Amino-8-oxo-9,10-epoxy-decanoic acid), which its side chain acts as an HDAC substrate mimic (129). Trapoxin and its synthetic derivatives have been shown to reversibly inhibit HDAC1 at low concentrations (nanomolar level). However, their inhibitory effects against HDAC6 are weak and irreversible (130,131). Substitution of the epoxyketone group in the trapoxin analogs resulted in a reduction of inhibition activity. Effects of trapoxin A on various subtypes of leukemia cell lines have been investigated. Kosugi *et al* (132) demonstrated that trapoxin A in combination with all-trans retinoic acid (ATRA) induce cell differentiation in both ATRA-sensitive and ATRA-resistant promyelocytic leukemia cell lines. Maeda *et al* (133) reported that compared with other HDACis, namely, sodium butyrate and romidepsin, trapoxin

A reduces HL60 cell viability although to a lesser extent. In addition, trapoxin A enhanced the expression of CD86, which acts as a co-stimulator for T-cell activation, suggesting that it can be developed as an immunotherapy agent and may become a novel drug for the treatment of leukemia.

Apicidin. Apicidin is a cyclic tetrapeptide derived from the fermenting broth of the fungus *Fusarium* spp. It was identified as a hemorrhagic factor and was shown to exhibit cytotoxic effect on human and mouse leukemia cell lines (134). Like that of trapoxin, its function is based on an epoxide functional group of Aoe, which mimics the ε-amino of lysine residues on histones. Apicidin acts as an HDAC inhibitor with cytotoxic effects on several cancer cell lines (135). It induced apoptosis in a Bcr-abl positive leukemia cell line (K562) and primary leukemia cells from patients with CML. Several reactions have been revealed to be associated with apoptosis induction in K562 cells, including increased histone H4 acetylation, disruption of mitochondrial function, downregulation of Bcr-abl expression, and activation of the caspase-cascade (136). These findings indicate that apicidin acts via an intrinsic apoptotic pathway. In addition, combining apicidin with the tyrosine kinase inhibitor imatinib, leads to significant enhancement of apoptotic effect in K562 cells. Apicidin can also induce apoptosis in Bcr-abl negative leukemia cell lines, namely Jurkat, U937 and HL-60 cells. However, a synergistic effect of the apicidin/imatinib combination was not observed (137). Previously, Ferrante *et al* (138) demonstrated inhibitory activity of apicidin against HDAC3, which is shown to be a positive regulator of the Notch signaling pathway. The study showed that HDAC3 deacetylated the Notch1 intracellular domain (NICD) protein preventing it from degrading. Apicidin inhibited HDAC3 activity and destabilized the NICD, which subsequently affected leukemia cell survival. Correspondently, compared with normal lymphoid cells, lymphoblastic leukemia cells had higher levels of HDAC3 expression. Treatment with apicidin resulted in decreased cell viability in human T-ALL cells and mantle cell lymphoma cells, but the apoptotic ratio and cell cycle distribution were not altered. These results suggested that apicidin could be a promising drug for the treatment of leukemias. However, additional mechanisms underlying antileukemic activity of apicidin still need to be explored.

FR235222. FR235222 is a cyclic tetrapeptide derived from the metabolite of the fungus *Acremonium* sp. It shares some structural similarities with trapoxin. FR235222 exhibits selective antiproliferative activity on T-lymphocytes and inhibits HDAC purified from human T-leukemia cells (Jurkat) and mouse lymphoma cells (EL-4) (139). This compound can inhibit HDACs in U937 cells, leading to increased levels of acetylated histone H4 and inhibition of cell proliferation. The antiproliferative effect was shown to be a consequence of cell cycle arrest at the G0/G1 phase influenced by p21 upregulation. Furthermore, in numerous types of leukemia cell lines, a low FR235222 concentration caused cell cycle arrest, whereas high concentrations of this compound triggered apoptosis. Both antiproliferative and apoptotic effects were found to be associated with the upregulation of annexin A1 expression (140). D'Acunto *et al* (141) developed a simplified analog of FR235222 called LGP1. They reported that, like FR235222, LGP1 stimulates histone H4 acetylation and induces U937 cell cycle arrest. It can induce tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-receptor expression, hence increasing cell sensitivity to TRAIL and reactivating caspase-dependent apoptosis.

5. Conclusion and future perspectives

Histone modification is an epigenetic regulator that plays important roles in the development and progression of leukemia. HDAC overexpression disrupts gene expression homeostasis associated with cell survival, proliferation and differentiation. Recent studies have shown that HDACis can be used to counteract HDAC activity leading to cell cycle arrest and apoptosis (142,143). Therefore, these compounds could be potential candidates for novel cancer drugs. The present review describes numerous peptides that act as HDACis as well as their therapeutic mechanisms and outcomes in cancer studies. Compared with small molecules, peptide inhibitors exhibit superior properties, especially high selectivity, offering the potential for reduced adverse effects and more precise targeting. Personalized therapy based on HDAC levels can be conducted to avoid pan-HDACis in favor of isoform-selective inhibitors, thereby improving safety while retaining antileukemic activity. Combinatorial strategies employing HDACis with other targeted therapies have also been explored, aiming to enhance treatment efficacy while overcoming resistance and minimizing toxicity. Translationally, it can be suggested that cyclic peptide HDACis can enhance multimodal therapy efficacy while maintaining acceptable safety profiles.

Notably, in clinical applications, numerous HDACis fail owing to their low therapeutic effectiveness and risk of adverse effects. Only two depsipeptides have been approved by the FDA and are commercially available. Major limitations of peptide drugs are that, compared with small-molecule inhibitors, they tend to have higher molecular weights and show lower oral bioavailability as a result of enzymatic degradation in the gastrointestinal tract. Their pharmacokinetics are often characterized by limited membrane permeability, relatively short half-lives, and challenges in achieving adequate systemic exposure. The enhancement of the pharmacokinetic properties of peptide drugs by promising strategies, including encapsulation, drug delivery and structure alteration, will be beneficial to their application in leukemia. Nano-delivery technology is widely employed to improve the bioavailability, antileukemic activity and tolerability of peptide-based HDACis, as exemplified by developments of nano-romidepsin (144,145). Furthermore, nanoparticles can be functionalized with targeting ligands, such as antibodies or aptamers that specifically bind to proteins presented in abundance on tumor cells (for example, transferrin receptor, CD20, CD33 and nucleophosmin). This approach may facilitate selective absorption of HDACis into target cells, resulting in increased local concentration. Homotypic targeting using nanoparticles coated with membranes from leukemia cells or stem cells is also an attractive option. Structural alteration, such as D-amino acid substitution, PEGylation, cyclization and cationization, can improve the stability and permeability of peptide drugs (146). Computational modeling technology has been used as a tool to

modify and optimize structure of HDACis based on molecular docking and binding interaction analysis to ensure drug selectivity and stability (147). Additionally, peptidomimetics can be designed and constructed to generate stabilized peptide HDACis with improved efficiency and selectivity (148). Future research should also focus on the design of customized peptide inhibitors enabling precise treatment for individuals.

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Authors' contributions

PP and YS conceptualized and designed the study and reviewed the manuscript. PP wrote the manuscript. YS acquired funding, prepared tables and figures, and revised the manuscript. Both authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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