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European Journal of Medical Research (2025) 30:169
https://doi.org/10.1186/s40001-025-02401-0

European Journal
of Medical Research

REVIEW

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Anticancer efficacy of Spiruchostatin A: current insights into histone deacetylase inhibition and oncologic applications

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Abstract

Spiruchostatin A also referred to as YM753 and OBP801, a cyclic peptide-based natural product derived from *Pseudomonas* sp., is distinguished by its potent inhibition of Class I histone deacetylases (HDACs). The modulation of epigenetic mechanisms by HDAC inhibitors is fundamental for altering gene expression related to cell growth, apoptosis, and differentiation, highlighting their potential in oncologic therapies. This updated review assesses the antitumor efficacy of Spiruchostatin A across diverse cellular and animal models, scrutinizing its viability as a therapeutic agent against various cancers. A systematic literature review was executed by searching databases such as PubMed/MedLine, Scopus, and Web of Science from October 2022 to February 2023. The inclusion criteria focused on studies involving Spiruchostatin A in the context of cancer treatment, including in vitro and in vivo models. The review concentrated on the compound's mechanistic action, biological activity, and clinical applicability. Spiruchostatin A has demonstrated significant antitumor activities, including inducing apoptosis and inhibiting tumor growth effectively in multiple models. Its therapeutic potential is particularly noted in synergistic applications with other anticancer agents, enhancing its efficacy. Mechanistically, the compound facilitates chromatin relaxation and transcriptional activation of key tumor suppressor genes through increased histone acetylation. Spiruchostatin A exhibits substantial potential as an anticancer agent through effective HDAC inhibition and subsequent epigenetic modifications of cancer cell biology. However, comprehensive clinical trials are imperative to validate its efficacy and safety profiles comprehensively. Future research is warranted to elucidate detailed molecular mechanisms and to develop biomarkers for predicting treatment response. Comprehensive longitudinal clinical studies are also critical to establish Spiruchostatin A's role within the broader oncological therapeutic regimen, along with the exploration of its analogs for improved therapeutic outcomes.

Keywords Anticancer, Epigenetics, HDAC inhibitor, Histone deacetylase, Spiruchostatin A, Therapeutic potential

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Introduction

Epigenetic mechanisms play an important role in cancer progression by regulating gene expression through modifications of chromatin structure [1–5]. Among the key epigenetic regulators are histone deacetylases (HDACs), which compact chromatin by removing acetyl groups from histones, thereby repressing gene transcription. In addition to promoting chromatin compaction and transcriptional inhibition, HDAC activity also affects acetylation processes that recruit bromodomain-containing proteins, which act as transcriptional co-activators [6]. Given their role in controlling oncogenic pathways, HDAC inhibitors have emerged as promising therapeutic agents in oncology. HDAC inhibitors can influence both histone and non-histone proteins, affecting various processes such as cell proliferation, DNA repair, and apoptosis. Recent research has demonstrated their efficacy in inducing cell cycle arrest, differentiation, and programmed cell death in cancer cells, with minimal impact on normal cells [7, 8]. In humans, 18 different HDACs have been identified and categorized into four major classes based on their homology with yeast deacetylases, as shown in Fig. 1. Class I includes HDACs 1, 2, 3, and 8, which utilize a Zn^{2+} binding mechanism. Class II, which also uses a Zn^{2+} binding mechanism, includes HDACs 4, 5, 6, 7, 9, and 10. Class IV, comprising only HDAC 11, also utilizes a Zn^{2+} binding mechanism. In contrast, Class III HDACs follow an NAD^{+}-dependent mode of action [9]. Additionally, non-acetyl acyl post-translational modifications (PTMs), such as crotonylation, butyrylation, and succinylation, have been recognized as important HDAC substrates, expanding the scope of HDAC function beyond histone deacetylation [10]. Notably, HDAC10 primarily functions as a polyamine deacetylase, acting on non-protein substrates and playing a distinct role in cellular metabolism compared to other HDAC family members [11].

HDAC inhibitors suppress cancer cell growth by targeting a specific subset of genes, approximately 3–7% of the genome, reflecting a focused mode of action [12]. They influence oncogenic pathways by modulating proteins like Bcl-6 (B-cell Lymphoma 6, a transcriptional repressor involved in certain cancers) and PML-RARα (promyelocytic leukemia-retinoic acid receptor alpha, a fusion protein associated with leukemia), and by reactivating tumor suppressor genes such as p21 Cip1/Waf1 (cyclin-dependent kinase inhibitor 1) and p16 INK4a (cyclin-dependent kinase inhibitor 2A), which are crucial for cell cycle regulation and apoptosis. HDACs contribute to cancer progression by altering gene expression related to cell survival and proliferation, and HDAC inhibitors counteract these effects through both histone and non-histone protein modifications, disrupting multiple pathways essential for cancer cell viability.

These HDACs primarily target chromatin and specific non-histone proteins that modulate critical oncogenic pathways, including the Bcl-6 pathway in certain cancers and the PML-RARα fusion protein in leukemia. The potential of HDAC inhibitors in cancer therapy lies in their ability to selectively reactivate tumor suppressor genes, such as p21 and p16, which regulate the cell cycle and promote apoptosis. Additionally, HDAC inhibitors can modulate the activity of several key proteins involved

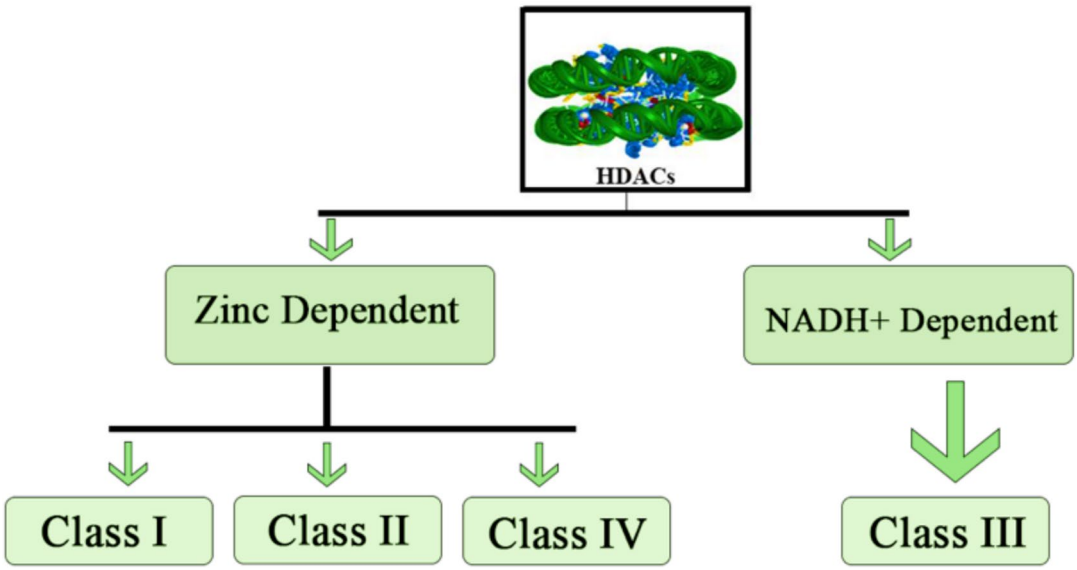

Fig. 1 HDACs classification

in tumorigenesis, including p53, E2F, and STAT3. By disrupting multiple pathways essential for cancer cell survival, HDAC inhibitors offer a multi-faceted approach to cancer treatment. Several HDAC inhibitors, such as SAHA (vorinostat) and FK228 (romidepsin), have shown promise in clinical trials. Vorinostat has been approved for treating recurrent cutaneous T-cell lymphoma, while romidepsin has received approval for treating both cutaneous and peripheral T-cell lymphoma [11]. These approvals underscore the clinical relevance of HDAC inhibitors and highlight their potential in treating hematological malignancies and solid tumors [11]. Spiruchostatin A (OBP-801), a novel HDAC inhibitor, demonstrates potent anticancer activity and is currently under clinical investigation. As a natural bicyclic depsipeptide, Spiruchostatin A selectively inhibits Class I HDACs, leading to increased acetylation of histones and non-histone proteins involved in cancer cell regulation. Recent studies indicate that Spiruchostatin A may be up to 50 times more potent than vorinostat in certain models [13]. As a natural bicyclic depsipeptide, Spiruchostatin A not only shows promise as a standalone agent, but is also being studied for its synergistic potential in combination therapies, particularly in challenging cancers such as triple-negative breast cancer. This review evaluates recent advancements in the understanding of Spiruchostatin A as an HDAC inhibitor, focusing on its mechanisms, biological activities, and therapeutic applications.

Review methodology

To gather a comprehensive overview of the anticancer properties of Spiruchostatin A, we conducted a systematic literature search across several databases including PubMed/MedLine, Scopus, Web of Science, and Google Scholar from October 2022 to February 2023. The search strategy employed MeSH terms and keywords relevant to the study focus: "Spiruchostatin A", "Histone Deacetylase Inhibitors", "Cancer Therapy", and "Oncology". The search was designed to capture both preclinical and clinical studies that describe the mechanism of action, biological activity, and potential clinical applications of Spiruchostatin A.

Studies were selected based on the following inclusion criteria: (i) published in English; (ii) involved Spiruchostatin A in the context of cancer treatment, including in vitro and in vivo studies, and clinical trials; (iii) reported on the biological mechanisms, therapeutic efficacy, or clinical outcomes related to the use of Spiruchostatin A.

Exclusion criteria were: (i) studies not specifically involving Spiruchostatin A; (ii) Non-peer-reviewed articles and conference abstracts due to the potential for preliminary data; (iii) studies focusing solely on other HDAC inhibitors without relevant comparisons or implications for Spiruchostatin A. Extracted information included study design, type of cancer investigated, experimental models (cell lines, animal models), dosage forms, administration routes, outcomes measured (e.g., cell viability, apoptosis induction, gene expression changes), and side effects or toxicity reported. The findings from the selected studies were synthesized in tables and figures to outline a comprehensive understanding of Spiruchostatin A's anticancer mechanisms, its efficacy across different cancer types, and its potential side effects and therapeutic windows. This synthesis aimed to provide a critical evaluation of the current landscape of Spiruchostatin A research and its future prospects in oncology.

Spiruchostatin A: a brief overview

Spiruchostatin A is a part of the FK288 family of natural products. It is found to have a strong ability to inhibit histone deacetylase HDAC and has also shown potential as a cancer-fighting agent. As natural bicyclic depsipeptides, FK288 and Spiruchostatin A exhibit unique structural features that contribute to their potent inhibition of Class I HDACs [14]. These compounds contain a characteristic cyclic depsipeptide backbone that enables them to form stable interactions with the active site of HDACs, leading to the inhibition of histone deacetylation. FK288, for example, acts as a prodrug, requiring reduction of a disulfide bond to activate its HDAC inhibitory activity, while Spiruchostatin A directly inhibits HDAC without requiring such activation [14]. This structural distinction suggests that Spiruchostatin A may provide a more rapid onset of HDAC inhibition, potentially improving its therapeutic efficacy. The structure–activity relationship of these compounds highlights the importance of their cyclic frameworks in facilitating HDAC binding and inhibiting cancer cell proliferation. Although, the production of Spiruchostatin A in the natural strain of *Pseudomonas sp.* Q71576 is limited. Initially, the Spiruchostatin A biosynthetic gene cluster (spi) was identified through genomic sequencing to enhance the production. The spi gene cluster and dep gene cluster in *Chromobacterium violaceum* no. 968 both contain a pathway regulatory gene, with genes encoding transcriptional activators of different classes [15].

Biochemical characterization

The structure of Spiruchostatin A is characterized by a 15-membered bicyclic depsipeptidase ring that contains elements of (3S,4R)-statine, D-cysteine, D-alanine, (3R,4E)-3-hydroxy-7-mercapto-4-heptonic acid, and a specific disulfide bond linkage, as shown in Fig. 2,,

which resembles FK228 which is a 16-membered bicyclic depsipeptide. It is structurally unique and biologically interesting compounds, making them attractive targets for total synthesis.

Spiruchostatin A and FK228, although both are potent inhibitors of Class I histone deacetylases (HDACs), exhibit distinct differences in structure and activation [16]. Spiruchostatin A has a 15-membered bicyclic depsipeptide ring, whereas FK228 (also known as Romidepsin) features a slightly larger 16-membered ring. Structurally, FK228 is a prodrug that requires reduction of a disulfide bond to release its active form, which is essential for binding to HDACs [17, 18]. In contrast, Spiruchostatin A does not rely on such activation, enabling direct HDAC inhibition upon administration; and this structural and functional distinction highlights Spiruchostatin A's unique mechanism of action and its potential advantages in cancer treatment [8, 19]. Simon et al., William et al., and Ganesan et al. have published three entire syntheses of FK228, whereas Wenworth, Janda, et al. have documented one total synthesis of FR 901375. Ganesan et al., Doi, Takahashi, et al., and Miller et al. have also published three complete syntheses of Spiruchostatin A. Previous research showed the entire synthesis of Spiruchostatin A, which aided in determining the stereochemistry of the chemical at the C5 position [20, 21].

Research indicates that Spiruchostatin A was completely synthesized through chemoselective macrocyclization utilizing a readily available, highly pure latent thioester. The synthesis method employed for Spiruchostatin A is notably different from those previously described. The macrocyclic alanine-cysteine amide connection is formed by initiating chemoselective transition to native chemical ligation using a latent thioester. The readily obtainable latent thioesters, acting as solid-phase linkers for cyclic peptidic compound synthesis, are constructed with a pendant carboxylic acid. This represents the first disclosure of such a moiety with enantiomeric purity [22]. Extensive research has been conducted on the production of these compounds and their analogues as potential anticancer agents due to their histone deacetylase (HDAC) inhibitory activity [23–25].

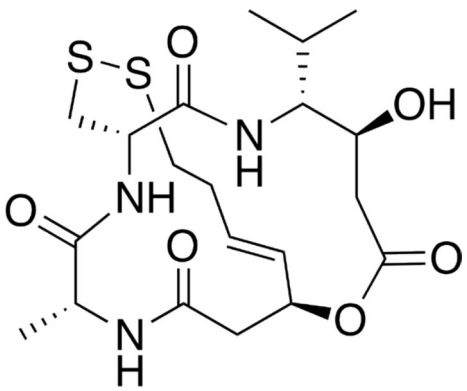

Fig. 2 Chemical structure of Spiruchostatin A. The structure features a complex arrangement of rings, including a macrocyclic lactone ring, which is critical for its inhibitory activity. Notable functional groups include ketones, esters, and multiple hydroxyl groups, which are essential for its binding affinity and specificity towards enzyme targets. The stereochemistry of each chiral center is clearly indicated, highlighting the molecule's precise three-dimensional configuration necessary for its biological activity

Bioavailability and pharmacokinetics of Spiruchostatin A

Spiruchostatin A, like many histone deacetylase (HDAC) inhibitors, faces challenges in terms of bioavailability due to its rapid metabolism and limited absorption. Studies have shown that after intravenous administration, Spiruchostatin A demonstrates a quick systemic clearance, which may impact its therapeutic window and effectiveness in clinical applications [26].

The low bioavailability observed is typical of depsipeptide structures, as they can be rapidly metabolized in the liver and excreted [27]. To address this, strategies such as nanoparticle conjugation and lipid-based formulations are under investigation, with the goal of enhancing stability, prolonging systemic circulation, and facilitating targeted delivery to tumor tissues. These approaches have shown promise in enhancing the pharmacokinetic profile of other HDAC inhibitors and are considered for improving Spiruchostatin A's clinical viability [28]. Moreover, Spiruchostatin A's direct mechanism of action on Class I HDACs, without requiring metabolic activation, contrasts with prodrug HDAC inhibitors such as FK228, suggesting it could be beneficial in achieving rapid therapeutic action if bioavailability challenges are addressed [29]. Further studies and clinical trials focusing on formulation optimization are necessary to enhance its bioavailability and assess its efficacy in vivo.

Microbial source and production optimization

Spiruchostatin A, a natural product with a molecular weight of 473 and a bicyclic depsipeptide structure, was found in the natural product library of Yamanouchi Pharmaceutical Co Ltd. It exhibited activity similar to that of transforming growth factor-beta [30]. Two novel compounds were identified from the fermentation broth of strain Q71576, which was obtained from various locations in Japan, through the screening process of over 40,000 microbial strains. These compounds were found to enhance the transcriptional activity of plasminogen activator inhibitor-1, which was named Spiruchostatin A and B [30]. The Q71576 strain is a microorganism that was obtained from the soil sourced in Nagano Japan. The Q71576 strain is a motile, Gram-negative bacterium with

one polar flagellum that was identified as Pseudomonas sp. after being isolated from the soil. The structure of the compound was verified through a chemical synthesis process carried out by Yurek-George and its team [25]. They also synthesized an alternative version of YM753, known as the epimer, and found that it did not have any effects on inhibiting cell growth. It was discovered that the (S) stereochemistry in the beta-hydroxy acid of the YM753 epimer was fundamental for HDAC inhibition. It was also observed that YM753 causes an increase in the amount of a certain type of modified histone and activates a specific gene promotor in breast cancer cells, indicating that the substance targets a specific enzyme involved in regulating gene expression, known as HDACs. The production of Spiruchostatin A in *Pseudomonas* sp. Q71576 is believed to occur in combined form of polyketide synthase (PKS) and non-ribosomal peptide synthetase (NRPS) pathways, similar to the mechanism of FK228 biosynthesis [31–33]. Efforts to develop Spiruchostatin A as a prospective natural product medicine for clinical application have included genetic mutations, metabolic process modification, and fermentation process optimization to boost production [34].

Efficacy and specificity of Spiruchostatin A as HDAC inhibitor

Spiruchostatin A has demonstrated potential efficacy as an anticancer agent, in various in vitro and in vivo studies of colon cancers [35, 36], leukemia cells [37], idiopathic pulmonary fibroblasts [38], endometrial carcinoma [39, 40], and renal cell carcinoma xenograft models [41].

Cell growth inhibition assay

Previous studies have demonstrated that histone deacetylase inhibitors can initiate the growth arrest in multiple forms of transformed cells and can inhibit the growth of human tumors in animal models, as shown in Fig. 3. As a result, these natural products have the potential as novel molecular targeted anticancer agents. Spiruchostatin A has been noticed as a compound that can increase gene expression and specifically inhibit class I HDACs during the screening process for activators TGF-β signaling [30]. The efficacy of this compound to suppress cancer cell development was investigated using a collection of 39 distinct human cancer cell lines from the Japanese Cancer Research Foundation [42]. Five breast malignancies, six central nervous system tumors, one melanoma, five ovary cancers, two kidney cancers, six stomach cancers, and two prostate cancers were used to create the cell lines. The inhibitory effects of the compound on the growth of human cancer cell lines were evaluated by determining the concentration at which 50% of the cells were inhibited (GI50) at various concentrations ranging from 1010 to 106 m using a panel of 39 cell lines from different origins and the comparison was made with the control. The results of the assay showed that the compounds tested had powerful effects on inhibiting the growth inhibition activity closely correlated with

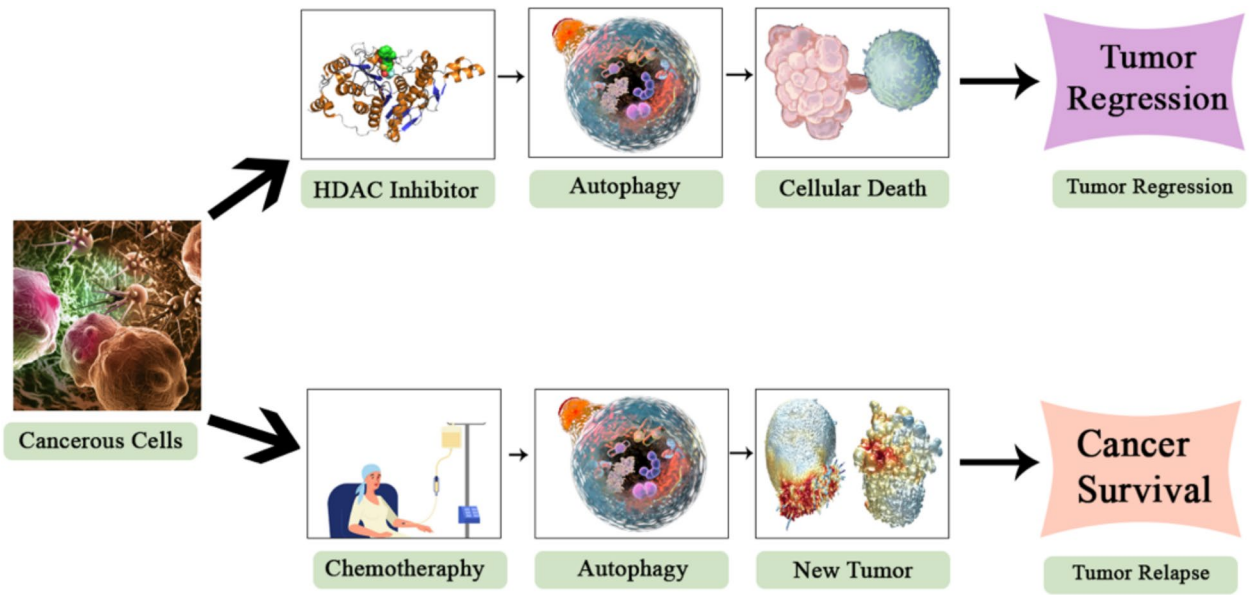

Fig. 3 Antitumor effect of HDAC inhibitors vs chemotherapy. HDAC inhibitors induce autophagy and cellular death, leading to tumor regression. In contrast, chemotherapy triggers autophagy but can lead to new tumor formation, resulting in cancer survival and relapse

their ability to inhibit HDAC1. All compounds examined also showed significant efficacy in the nanomolar range, correlating to their capacity to inhibit HDAC1. The order of potency was 2 (5.6 nm), 3 (6.2 nm), 52 (7.6 nm), > 1 as evaluated by the MG-MID value, which is a measure of the mean value of the concentration inducing 50% cell growth inhibition (15 nm). Spiruchostatin A looks to be a highly attractive candidate for the development of novel anticancer medicines that target class I HDAC based on its combination of HDAC inhibitory and antiproliferative action. Nobuaki Shindoh and colleagues published a study titled "Spiruchostatin A (YM753), a novel histone deacetylase inhibitor, exhibits anticancer activity by inducing selective and sustained accumulation of acetylated histones in tumors in the WiDr xenograft model." Both in vitro and in vivo studies have confirmed the anticancer properties of HDAC enzyme inhibitors. The natural compound YM753, derived from bacteria, possesses both a disulfide bond and the HDAC enzyme. In tumor cells, YM753 underwent rapid reduction, resulting in an accumulation of acetylated histones, inhibition of tumor cell proliferation, and cancer-specific cell death. In vitro tests using Spiruchostatin A (YM753) demonstrated prolonged deposition of acetylated histones in WiDr human colon tumor cells. The continuous accumulation of acetylated histones in malignant cells following in vivo YM753 treatment of mice with WiDr tumor xenografts significantly reduced tumor development. These studies suggest that Spiruchostatin A (YM753), as a new HDAC inhibitor, exhibits promising pharmacologic and pharmacokinetic characteristics, potentially making it a potent anticancer medication [35]. Simon J. Crabb and colleagues conducted research on the characterization of the in vitro effects of Spiruchostatin A. The in vitro actions of Spiruchostatin A were thoroughly characterized. Spiruchostatin A functioned as a prodrug that required reduction to become active and was a potent in vitro inhibitor of class I HDAC. The development of several cancer cell lines was significantly inhibited by Spiruchostatin A. Additionally, Spiruchostatin A induced cell cycle arrest, differentiation, and cell death in MCF7 breast cancer cells. While histone acetylation was briefly elevated by the hydroxamate HDI, it was more persistently induced by Spiruchostatin A and FK228, respectively. Changes in the kinetics of histone acetylation due to HDI were associated with substantial differences in the activation or inhibition of certain target genes, as revealed through microarray analysis of HDI-targeted genes. The findings demonstrated that Spiruchostatin A is a powerful class I HDAC inhibitor and an antitumor agent. Variations in the kinetics of HDI action may be important for the clinical use of these substances [23]. According to another research, the inhibition of HDAC enzymes can induce various changes in genetic expression that affect the cell cycle progression. This can result in cell cycle arrest at the G1 or G2/M phase, which can lead to cell death or halt the uncontrolled growth seen in cancer cells. However, the effect of HDIs on the cell cycle can vary depending on various factors, such as the specific HDI used, the dose, and the cell line model system being studied. Therefore, further research is required to fully understand the mechanisms by which HDIs impact the cell cycle and the most effective use of HDIs in clinical settings [4, 31, 47]. In another study, the HDAC inhibitor Spiruchostatin A was fully synthesized, and its biological activity was initially evaluated. A convergent and unified method was successfully employed to manufacture Spiruchostatin A. The depsipeptides were synthesized, and the examination of cell-growth suppression along with HDAC inhibitory assays helped to determine their potency, revealing several novel structure–activity relationships. Furthermore, Spiruchostatin A demonstrated extraordinarily high selectivity and potent cell-growth inhibitory action against class I HDAC1 at nanomolar concentrations [43]. Researchers have completed the full synthesis of Spiruchostatin A. After successfully synthesizing this histone deacetylase inhibitor, efforts shifted towards developing a combinatorial library of Spiruchostatin A analogues. Key steps in this process included macrolactonization using the Shiina technique and the acetate aldol reaction facilitated by a Zr-enolate [44]. Iijima, Yusuke, et al. demonstrated how to synthesize Spiruchostatin A, a cyclic depsipeptide HDAC inhibitor, using solid-phase techniques. The synthesis of Spiruchostatin A required three additional steps starting from 4-amino-3-hydroxy-5-methylhexanoic acid. The first step involved the formation of an intramolecular disulfide bond within the molecule. The second step entailed solid-phase peptide elongation with D-cysteine and D-alanine, incorporating these amino acids into the molecule through solid-phase synthesis methods. The final step was solution-phase macrolactonization, which created a macrocyclic lactone ring structure by reacting the elongated molecule with a lactone-forming agent. These steps are typical in the synthesis of HDAC inhibitors that possess specific properties and activities, making them suitable for use as drugs or other biologically active compounds [45]. Histone deacetylases (HDACs) are considered to be potential targets for the treatment of cancer because they are important in the regulation of chromatin's post-translational modification [46]. Spiruchostatin A, a new gene expression enhancer produced by Pseudomonas sp., was discovered by researchers in a study. They have novel 4-amino-3-hydroxy-5-methylhexanoic acid residues in

bicyclic depsipeptides [30]. Another research examined the whole production of the Spiruchostatin A. By using this synthesis, the whole structure of Spiruchostatin A is clearly verified. The Nagao auxiliary's dual role as an acylating agent and chiral auxiliary for creating acetate aldols is remarkable. Clinical studies have begun for the anticancer drugs FK228 and, more recently, Spiruchostatin A. This approach makes it possible to develop and assess synthetic analogues [25].

HDAC inhibition assay

It has been established that inhibiting class I HDACs is a beneficial approach for developing anticancer drugs, while inhibiting class II HDACs may lead to unwanted side effects. Research indicates that compounds like Spiruchostatin A and FK228 exhibit strong selectivity for HDAC class I over HDAC class II [47].

Antitumor mechanisms of Spiruchostatin A (YM753/OBP801)

Spiruchostatin A (YM753), also known as OBP801, is a highly potent inhibitor of class I histone deacetylases (HDACs), fundamental for regulating gene expression through epigenetic modifications [48]. By targeting HDACs 1, 2, 3, and 8, Spiruchostatin A effectively prevents the deacetylation of histone proteins. This action results in the relaxation of chromatin, enhancing the transcription of tumor suppressor genes and leading to increased expression of genes involved in cell cycle arrest, apoptosis, and differentiation. These are key processes essential for controlling tumor proliferation and progression. The pharmacological and biological properties of the histone deacetylase (HDAC) inhibitors play an important role in the regulation of gene expression. Acetylated lysine residues on histones are hydrolyzed by zinc metalloenzymes known as HDAC enzymes [49]. Human HDACs have been found to exist in 18 different forms, and using their similarity to yeast deacetylase as a guide, they were categorized into four groups [50]. Zn-binding enzymes make up Class I, II, and IV HDACs, while NAD-dependent mode of deacetylation include class III HDAC enzymes [49, 50]. Spiruchostatin A is an effective Class I HDAC inhibitor [25]. Spiruchostatin A is a natural cyclic compound that composed of depsipeptide and cysteine residues. It was first discovered in Pseudomonas sp. during research for cancer treatment medications that could imitate the antiproliferative actions of the TGF-B1 by stimulating the genes that halted the cell growth and proliferation [30]. HDAC are a class of drugs that target the activity of HDAC enzymes. HDAC enzymes play role in regulating the expression of genes by modifying the acetylation status of histones, the proteins around which DNA is wrapped. By inhibiting HDAC enzymes, HDAC inhibitors can increase the acetylation of histones and thereby change the expression of genes that control processes such as cellular proliferation, differentiation, and apoptosis. This makes HDAC inhibitors a promising therapeutic option for a variety of diseases, including cancer, neurological disorders, and inflammation.The N-terminal of the histones proteins are often modified by the process of deacetylation which involve the removal of acetyl group from the lysine amino acid residues to inhibit the activity of histone. Histone acetylation and other post-translational changes greatly influence how chromatin is packaged, controlling the expression of genes by creating a "histone code" that transcription factors can interpret [51, 52]. Histones and other proteins become hyperacetylated as a result of HDIs' interference with HDAC activity. With relatively little impact on normal cells, HDI causes inhibition, cellular death, and differentiation in a variety of susceptible cancerous cells [21, 53–55]. A number of enzymes modify the histone terminal tails, play a vital role in the regulation. The modifications includes phosphorylation, acetylation, and methylation. These acetyl groups are removed by the histone deacetylase enzyme. The proliferation of both healthy and malignant cells is halted by histone acetylation, which is increased by histone deacetylase inhibitors. Histone acetyl transferases (HATs), on the other hand, acetylate the lysine amino-terminal tails of these histones [21, 56]. HAT and HDAC, respectively, acetylate and deacetylate the core histones on the N-terminal tail region of the chromatin (Yurek-George, 2004, AW, 1997). Higher-order chromatin folding is hampered by acetylation of the histone tails, which also makes chromatin more soluble under physiological ionic conditions (Yurek-George, 2004). HDAC inhibitors have been demonstrated to bind specifically to the HDAC active site, obstructing substrate access and causing a build-up of acetylated histones. These HDAC inhibitors are currently being evaluated for the treatment of various types of solid and hematological cancers. They induce differentiation, suppress cell proliferation, and induce apoptosis of tumor cells in cultures and animal models [21, 57] (Fig. 4).

Spiruchostatin A demonstrated significant efficacy in inducing apoptosis in U937 human myelomonocytic lymphoma cells in a time- and dose-dependent manner at concentrations from 3 to 100 nM [13]. Notably, at

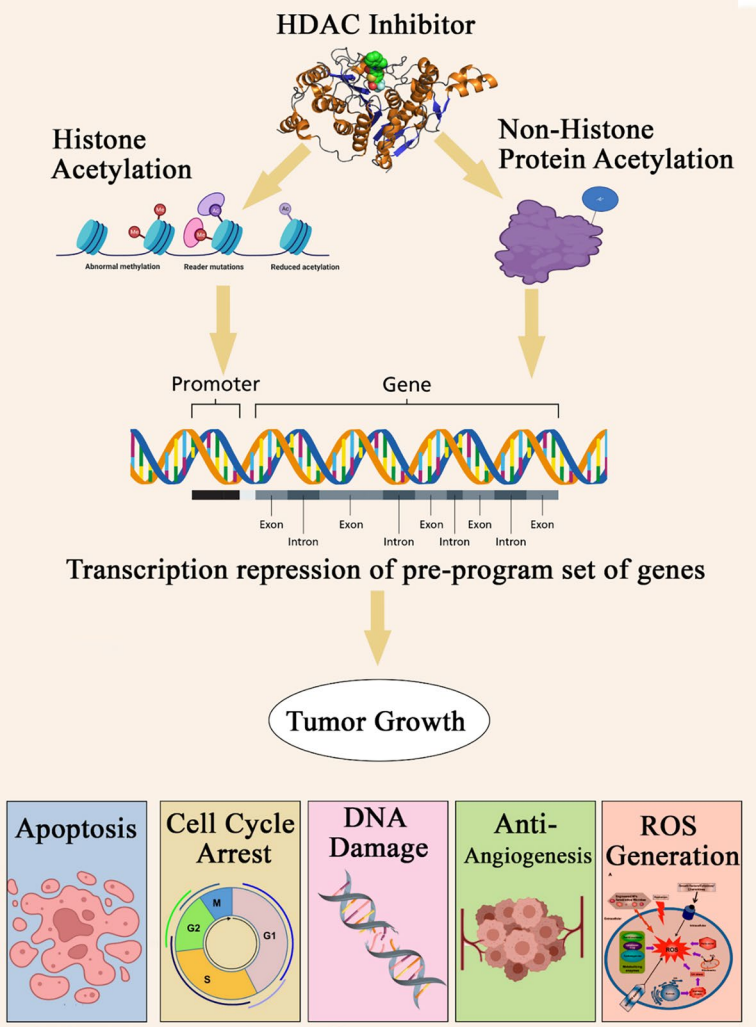

Fig. 4 Anticancer mechanism of action of Spiruchostatin A. The figure delineates the molecular mechanism of action of Spiruchostatin A as an inhibitor of histone deacetylases (HDACs). Spiruchostatin A binds to the active sites of Class I HDAC enzymes, leading to a marked increase in the acetylation levels of histone and non-histone proteins. Such hyperacetylation disrupts the typical chromatin compaction, facilitating a more open chromatin state that modulates gene expression patterns. The diagram specifically illustrates the resultant transcriptional repression of genes that are critical in oncogenic pathways, effectively impeding tumor growth and progression. Downstream effects of this epigenetic modulation include the induction of apoptosis, arrest of the cell cycle, DNA damage, anti-angiogenesis, and the generation of reactive oxygen species (ROS), each contributing to the cytotoxic profile against neoplastic cells. Collectively, these pathways underscore the comprehensive anti-tumorigenic properties of Spiruchostatin A, highlighting its potential as a robust therapeutic agent in oncology. *DNA* deoxyribonucleic acid, *HDAC* histone deacetylase, *ROS* reactive oxygen species

30 nM, it significantly increased intracellular ROS formation, activated caspases, and released cytochrome-c from mitochondria to cytosol. Furthermore, it raised acetylated histone H3 and H4 levels over time, enhancing the sub-G1 cell population from 2.3 to 27% [13].

In WiDr xenograft nude mice, a single intravenous dose of Spiruchostatin A at 3 mg/kg notably inhibited tumor growth by promoting the accumulation of acetylated histones and the p21WAF1/Cip1 protein. This effect persisted with histone H3 and H4 acetylation observable even 72 h post-administration, demonstrating the long-lasting action of the drug. Plasma concentrations peaked at 558 nM shortly after administration and reduced to 15 nM within 15 min, indicating rapid metabolism and conversion to its active form, RedYM [36]. A comprehensive overview of the mechanistic actions and therapeutic impacts of Spiruchostatin A is detailed in Table 1.

Table 1 The mechanistic action and antitumor efficacy of Spiruchostatin A (YM753/OBP801)

Key aspects	Mechanism	Biological outcome	References
HDAC inhibition	↓Deacetylase activity	Inhibits Class I HDACs ↑Histone acetylation and changes in chromatin structure, which affect gene expression regulation	[48]
Gene expression modulation	↑Transcription	Promotes increased transcription of tumor suppressor genes and influences genes involved in cell cycle arrest, apoptosis, and differentiation	[49, 50]
Biochemical interaction	Binding to HDAC active sites	Binds to the active sites of HDAC enzymes, ↓acetylation of histone and non-histone proteins ↓Chromatin accessibility, ↓gene expression	[25]
Origin and pharmacological discovery	Derived from microbial metabolism	Discovered in Pseudomonas sp., inspired by research on TGF-β1's antiproliferative effects to regulate cell growth through gene expression modulation	[30]
Therapeutic implications	Epigenetic regulation of gene expression	↑Potential for therapeutic applications in oncology, neurology, and anti-inflammatory treatments through epigenetic modulation of gene expression	[51, 52]
Clinical impact of HDAC inhibition	↑Hyperacetylation	↑Hyperacetylation ↑Apoptosis, ↓differentiation of tumor cells minimally affecting non-cancerous cells	[21, 53]
Preclinical evidence	↑Apoptosis ↓Tumor growth	↑Apoptosis in U937 cells ↓Tumor growth in WiDr xenograft nude mice through ↓Histone acetylation, ↓p21WAF1/Cip1	[13, 36]

Synergistic anticancer effects with other therapeutics

Spiruchostatin A has demonstrated significant synergistic effects when combined with a variety of other anticancer agents, highlighting its potential to improve treatment outcomes across different cancer types. These combinations generally result in enhanced apoptosis, reduced tumor growth, and improved survival rates in preclinical models. A recent study investigates the efficacy of combining the novel histone deacetylase (HDAC) inhibitor OBP-801/YM753 with the PI3K inhibitor LY294002 in targeting human endometrial carcinoma cells, specifically HEC-1A cells. The study is motivated by the frequent overactivation of the PI3K/Akt pathway in endometrial carcinoma due to mutations in key regulatory genes like PIK3CA and PTEN [39]. The therapeutic potential of this combination was assessed through a series of in vitro and in vivo experiments. In vitro assays, including WST-8 and colony formation tests, showed that the combination of OBP-801/YM753 and LY294002 notably inhibited cell growth more effectively than either agent alone. This enhanced effect was attributed to a significant increase in apoptosis, facilitated by the induction of Bim, an apoptosis promoter, and the accumulation of reactive oxygen species (ROS) within the cells. Western blotting confirmed the upregulation of apoptosis-related proteins, reinforcing the mechanistic basis for cell death [39]. In vivo, the combination treatment markedly reduced tumor volume in female BALB/c nu/nu mice engrafted with HEC-1A cells, indicating a robust antitumor response. Mice received treatments three times a week for 2 weeks: a control diluent, OBP-801/YM753 (5 mg/kg), LY294002 (25 mg/kg), or their combination. OBP-801/YM753 was injected into the tail vein, and LY294002 was administered intraperitoneally. Notably, the combination of OBP-801/YM753 and LY294002 demonstrated a more potent apoptosis-inducing effect compared to the combination of SAHA (another HDAC inhibitor) with LY294002, suggesting a superior therapeutic profile for OBP-801/YM753 in this specific cellular context. The findings suggest that the synergistic interaction between OBP-801/YM753 and LY294002 could represent a promising new therapeutic strategy for treating endometrial carcinoma, emphasizing the critical role of Bim induction and ROS accumulation in mediating the observed anticancer effects [40]. Another study demonstrated that the novel histone deacetylase (HDAC) inhibitor OBP-801 and the phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002 acted synergistically to inhibit cell growth and induce apoptosis in renal cell carcinoma (RCC) cells. This synergy was particularly relevant given the known resistance of RCC to conventional cancer therapies, including radiation and chemotherapy, and the tendency for patients to develop resistance to targeted therapies over time [41]. The combined application of OBP-801 and LY294002 triggered significant apoptosis through the activation of caspases 3, 8, and 9. The presence of zVAD-fmk, a pan-caspase inhibitor, significantly

reduced this apoptotic response, confirming the caspase-dependent nature of apoptosis induced by these agents. Treatment elevated intracellular ROS levels, essential for inducing apoptosis. Administration of N-acetyl-L-cysteine (NAC), a radical scavenger, was found to inhibit both ROS accumulation and the subsequent apoptotic processes, indicating a critical role of ROS in the drugs' mechanism of action. Levels of survivin and XIAP, proteins that inhibit apoptosis, were markedly decreased following treatment. This effect was reversible with NAC administration, further linking the apoptotic effects of the drug combination to ROS activity. Experiments involving transient transfection with survivin and XIAP suggested that elevated levels of these proteins could diminish the apoptosis induced by the drug combination, pointing to a potential resistance mechanism. Moreover, OBP-801 was shown to be more effective than SAHA, another HDAC inhibitor, in combination with LY294002 in reducing levels of survivin and XIAP and in inducing apoptosis [41]. In a study conducted by Furutani et al., it has been explored the effectiveness of the novel histone deacetylase (HDAC) inhibitor OBP-801/YM753 in enhancing the therapeutic impact of 5-fluorouracil (5-FU) and radiation on esophageal squamous carcinoma cells, specifically the KYSE170 cell line [58]. Previous studies have shown HDAC inhibitors can augment the effects of 5-FU in various cancers, but their role in enhancing 5-FU combined with radiation had not been previously reported. The research findings indicated that the combined application of OBP-801/YM753 and 5-FU significantly inhibited cell growth more than treatment with 5-FU alone. Moreover, the addition of radiation to this combination further inhibited colony formation, suggesting a synergistic effect. Western blot analysis revealed that OBP-801/YM753 effectively suppressed thymidylate synthase expression, an enzyme typically upregulated by 5-FU, pinpointing a possible mechanism for the enhanced therapeutic outcome. These results suggest that the triple combination of OBP-801/YM753, 5-FU, and radiation could be a promising therapeutic strategy for treating patients with esophageal squamous carcinoma [58]. Ono et al., explored the synergistic effects of combining the novel histone deacetylase (HDAC) inhibitor OBP-801 with eribulin on triple-negative breast cancer (TNBC) cells. TNBC is recognized as the most aggressive subtype of breast cancer, with eribulin already approved for treating metastatic breast cancer based on the EMBRACE trial's findings, particularly showing promise in TNBC subgroups. Despite this, TNBC's prognosis remains poor, driven by its complex molecular traits, underscoring the critical need for more effective treatments [59]. The study focused on assessing whether OBP-801 could enhance the antitumor activities of eribulin. Researchers conducted cell growth analyses and flow cytometry to examine the effects on cell cycle dynamics and apoptosis induction. Additionally, Western blot analyses were employed to explore the underlying mechanisms of the treatment's effectiveness. The results revealed that the combination of OBP-801 and eribulin not only synergistically inhibited the growth of TNBC cells, but also significantly enhanced apoptosis compared to either treatment alone. Notably, the study discovered that while eribulin alone upregulated survivin—a protein that inhibits apoptosis—OBP-801 could substantially counteract this effect. Furthermore, the combination treatment effectively suppressed Bcl-xL and the MAPK

Table 2 Synergistic anticancer effects of Spiruchostatin A (OBP-801/YM753) combined with various therapeutics

Study focus	Combination	Effectiveness	Mechanism	References
Endometrial carcinoma	OBP-801/YM753 + LY294002	↑Apoptosis ↓Tumor growth More effective than either agent alone or SAHA + LY294002	↑Induction of Bim, ↑ ROS, upregulation of apoptosis-related proteins	[39, 40]
Renal cell carcinoma	OBP-801/YM753 + LY294002	↑Apoptosis More effective than SAHA + LY294002	↑Caspases 3, 8 and 9; ↑ROS ↓ N-acetyl-L-cysteine ↓survivin, ↓XIAP	[41]
Esophageal squamous carcinoma	OBP-801/YM753 + 5-FU + radiation	↓Cell growth ↓Colony formation enhanced by the addition of radiation	↓ Thymidylate synthase expression	[58]
Triple-negative breast cancer	OBP-801/YM753 + eribulin	↓Tumor growth ↑Apoptosis Counteracted eribulin-induced upregulation of survivin	↓ Bcl-xL ↓MAPK	[59]

5-*FU* fluorouracil, *Bcl-xL* B-cell lymphoma-extralarge, *Bim* Bcl-2-like protein 11, *HDAC* histone deacetylase, MAPK mitogen-activated protein kinase, *NAC* N-acetyl-L-cysteine, *PI3K* phosphoinositide 3-kinases, *RCC* renal cell carcinoma, *ROS* reactive oxygen species, *SAHA* suberoylanilide hydroxamic acid, *TNBC* triple-negative breast cancer, *XIAP* X-linked inhibitor of apoptosis protein

pathway, indicating a potent inhibitory effect on important survival mechanisms in TNBC cells. This study highlights the potential of combining OBP-801 with eribulin as a more effective therapeutic strategy for managing triple-negative breast cancer, offering a promising direction for future clinical advancements [59] (Table 2).

Toxicity, side effects and safety

The tolerability of Spiruchostatin A and other HDI is generally good. Thrombocytopenia, tiredness, nausea, and vomiting are common toxicities [60–62]. Early-phase trials have revealed modest single-agent activity to date, and clinical trials are evaluating for the combined use with both traditional cytotoxic and molecular targeted therapies [63]. FK228 and Spiruchostatin A were shown to be more effective than hydroxamate and benzamide HDI in a panel of human solid tumor cell lines [23]. The development of fibrotic fibroblasts was reduced by Spiruchostatin A in a time- and dose-dependent manner. Even at high concentrations of Spiruchostatin A, no cytotoxicity was seen, despite the fact that Spiruchostatin A was seen to limit proliferation [64]. Studies revealed that the depsipeptides of Spiruchostatin A may contribute to both the patterns of toxicity and their efficacy by promoting long-lasting acetylation reactions. This could be significant for dose plans employed in HDI clinical trials. The optimal duration for HDAC inhibition, as well as whether it should be done constantly or periodically, have yet to be identified. Studying these characteristics during clinical development might help to balance the trade-off between efficacy and potential negative effects. Moreover, scheduling in conjunction with other anticancer medications may have consequences. Scheduling in cell-based assay systems has been demonstrated to be important for maximizing the synergism of some chemotherapeutic combinations [65–67].

Therapeutic perspectives, limitations and clinical gaps

HDAC inhibitors are a class of drugs, which disrupt the cell cycle, are currently undergoing early clinical studies [68]. Each of these potential cancer treatments is still in clinical testing, so it is unclear how effective they will be. Natural products serve as invaluable resources for discovering novel chemical building blocks for therapeutic applications and exploring chemical diversity [69, 70]. Currently, 70% of recommended drugs come from natural sources or products derived from them [71, 72]. Many of the most widely used cancer drugs, such as vinca alkaloids, taxanes, and anthracyclines, are derived from natural sources or based on natural product structures. Additionally, many new cancer treatments being developed are also based on natural products or their derivatives. This highlights the continued importance of natural products in the search for new cancer treatments. Spiruchostatins A–D exhibit strong selectivity for class I HDAC has low nanomolar IC_{50} values, while HDAC6 has values in the hundreds [43, 73]. Since Spiruchostatin A practically lost all of its inhibitory potency when it was not reduced, these values were achieved in a reducing environment in order to obtain the open dithiol [23]. Crabb et al. demonstrated in 2008, four human carcinoma cell lines including MCF7 and breast (BT474); ovarian (A278); colon (HT29) showed substantial antiproliferative activity, [43] and, nearly all of the 39 human cancer cell lines examined with Spiruchostatin A and B by Narita et al. revealed comparable results [73]. Using the average IC_{50} value across all analyzed lines, potency can be ranked [73]. Rehman et al. studied the role of Spiruchostatin A in human lymphoma U937 cells in 2014. They discovered that the chemical produced apoptosis in the treated cells, increasing histone H3 and H4 acetylation and the proportion of cells in the G1 cell phase [74]. The researchers discovered that the generation of reactive oxygen species was needed for the development of apoptosis and that the inhibitors boosted the expression of caspase-3 and caspase-8, which are important for the signaling cascades that result in apoptosis. Numerous malignancies have been identified to have various HDACs overexpressed [75]. For instance, prostate cancer cells overexpress HDAC1 [76], while colorectal and gastric carcinomas frequently overexpress HDAC2 [77]. Cancer therapies for cutaneous T-cell lymphoma and other malignancies are already clinically licenced for HDIs such SAHA and FK228, among others. They have a particular toxicity towards tumor cells while generally being harmless to healthy cells and a variety of molecular pathways are successfully activated by them to produce their anticancer actions are the essential characteristics of their therapeutic importance [78]. HDAC inhibitors have been found to reduce the proliferation of the human cancer xenografts and to inhibit the proliferation of a number of altered cell types. It follows that highly effective and narrowly focused HDAC inhibitors would be great choices for cutting-edge molecularly tailored anticancer medications [49]. For example, HDAC5 and HDAC9 are thought to reduce cardiac hypertrophy [79]. The growth and survival of cancer cells are assumed to be significantly preserved by class I HDACs [80–82]. A variety of solid and hematological malignancies are being treated in clinical trials utilizing different HDAC inhibitors [83]. For the treatment of cutaneous T-cell lymphoma, SAHA (suberoylanilide hydroxamic acid) just

got FDA approval after the phase I/II studies showed it to have potent anticancer effects in individuals with hematologic and solid malignancies [60, 84–86]. In a clinical trial, FK228 showed exceptional efficacy against cutaneous and peripheral T-cell lymphomas. These results demonstrate the significant potential of HDAC inhibitors as anticancer drugs [83]. Although FK228 (Romidepsin) has progressed further in clinical development, Spiruchostatin A exhibits unique characteristics that may make it a promising candidate for anticancer therapy [17]. Unlike FK228, which requires reduction to release its active form, Spiruchostatin A directly inhibits Class I HDACs, potentially offering a more rapid therapeutic effect. Additionally, Spiruchostatin A has shown potent anticancer effects across various types of cancer cells, including breast, ovarian, and colorectal cancers, and demonstrates a selective HDAC inhibition profile that may reduce off-target effects [13]. These features highlight its potential advantages and justify further clinical exploration.

Several limitations and clinical gaps warrant further investigation to optimize its clinical utility:

i. The precise mechanisms by which Spiruchostatin A selectively targets cancer cells remain inadequately defined. Detailed studies are required to elucidate the drug's epigenetic effects on gene regulation and its selective impact on cancer versus normal cells.
ii. There is notable variability in Spiruchostatin A's efficacy across different cancer types and even among cell lines of the same cancer. This variability suggests a need for identifying predictive biomarkers that could enhance patient selection and therapeutic outcomes.
iii. Comprehensive long-term safety data and optimal dosing protocols are lacking. Future studies should focus on establishing these parameters to reduce toxicity and maximize efficacy.
iv. The development of resistance to Spiruchostatin A has not been thoroughly investigated. Research into potential resistance mechanisms and strategies to overcome or prevent resistance is critical. Comparative studies are essential to define Spiruchostatin A's place in the therapeutic landscape.
v. Most findings are derived from preclinical models, which may not fully mimic human pathophysiology. Bridging these results to clinical effectiveness requires carefully designed clinical trials. There is a lack of comprehensive results from ongoing clinical trials. Longitudinal studies are necessary to assess long-term efficacy and safety, providing important data for clinical application.

Conclusion and future prospects

The exploration of Spiruchostatin A as an HDAC inhibitor has uncovered significant potential in the realm of cancer therapy. This compound, with its potent epigenetic modulation capabilities, has demonstrated efficacy across various in vitro and in vivo models, highlighting its role in promoting apoptosis, cell cycle arrest, and gene expression modulation conducive to cancer suppression. However, the transition from promising preclinical results to effective clinical application necessitates a concerted effort to address the gaps and limitations identified in the research to date. Future research should prioritize a deeper mechanistic understanding of Spiruchostatin A's selective anticancer activity. This involves not only mapping its impact on histone acetylation, but also exploring its influence on non-histone proteins and other epigenetic markers. Such studies will help tailor therapies to the specific epigenetic landscapes of different cancers and potentially reduce the variability in treatment outcomes. Moreover, the development of robust biomarkers for predicting therapeutic response will be important. Biomarker-driven trials can enhance patient selection processes, ensuring that Spiruchostatin A is administered to individuals most likely to benefit, thereby optimizing therapeutic outcomes and minimizing unnecessary exposure to potential side effects. Clinical trials remain the cornerstone for translating Spiruchostatin A's laboratory success into a clinically viable treatment option. Future trials should be designed to not only confirm efficacy and safety, but also to compare Spiruchostatin A with existing HDAC inhibitors and standard therapies. This comparative analysis will help position Spiruchostatin A within the current treatment paradigm and might suggest combination strategies that could mitigate resistance mechanisms and improve patient outcomes. In addition, long-term studies are needed to assess the durability of responses to Spiruchostatin A and to monitor for late-emerging side effects or resistance patterns. Understanding these aspects is vital for developing effective dosing regimens and for integrating Spiruchostatin A into multimodal cancer treatment protocols. The exploration of Spiruchostatin A also opens doors to the synthesis and testing of analogs that may offer improved efficacy and safety profiles. The chemical flexibility of Spiruchostatin A provides a valuable template for the development of next-generation HDAC inhibitors. In conclusion, while Spiruchostatin A presents a promising therapeutic pathway, the full realization of its potential will depend on addressing the current gaps through rigorous research and clinical testing. The future of Spiruchostatin A, like many novel therapeutics, will be shaped by our ability to integrate it effectively within the broader context of cancer treatment, leveraging its unique properties to

offer better outcomes for patients facing this challenging disease.

Abbreviations

CTCL	Cutaneous T-cell lymphoma
FDA	Food and Drug Administration
HATs	Histone acetyltransferases
HDAC	Histone deacetylase
HDI	Histone deacetylase inhibitor
MCF7	Michigan Cancer Foundation-7
NRPS	Non-ribosomal peptide synthetase
PKS	Polyketide synthase
PML-RAR	Promyelocytic leukemia/retinoic acid receptor alpha
PTCL	Peripheral T-cell lymphoma
SAHA	Suberoylanilide hydroxamic acid
Spiruchostatin A	Spiruchostatin A
TGF- β	Transforming growth factor-β
TNBC	Triple-negative breast cancer
α-SMA	Alpha-smooth muscle actin

Author contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas that is revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and confirming to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

Funding
Not applicable.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 21 May 2024 Accepted: 21 February 2025
Published online: 14 March 2025

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