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Review of Histone deacetylase (HDAC) inhibitors in treatment of chronic diseases

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Abstract
Histone deacetylase (HDACs) are conserving evolutionary enzymes that work by removing acetyl groups from histones and other protein regulatory elements, with functional effects on chromatin remodel and gene express patterns. Here, we present a review of the mostly recent information on the zinc-dependent HDAC protein family that has been accumulated across several animals, tissues, and human disorders, with an emphasis on the function of HDAC inhibitors as anticancer drugs. We will look at the chemical differences between various HDACs and talk about how they participate in chromatin-binding and regulatory complexes in the human interactome.

Keywords: chronic, deacetylase, diseases, histone and treatment

Introduction
One of the most significant medical advancements in the previous several decades has been chemotherapy for cancer. The medications utilized for this therapy have a limited therapeutic index, and the results are frequently just palliative and unreliable. Although targeted at specific bio macromolecules, such methods do not distinguish between cancer and non-cancerous cells that divide quickly. The more recent development of targeted treatment, which focuses on cancer-specific targets and signaling pathways, has less extensive nonspecific mechanisms. Numerous studies have shown that epigenetic pathways plays a significant roles in the genesis of cancer. Epigenetic mechanisms are also involved in carcinogenesis and cannot be solely explained by genetic changes (DNA methylation, histone modifications and non-coding RNA deregulation). Lysine deacetylation of H3 and H4 histone, one of histone modifications, results in chromatin decondensation [1]. Numerous anti-oncogenes and DNA repair genes are upregulated as a result of these changes, which also affect gene transcription. As a result, multiple studies have identified the epigenetic processes as potential therapeutic targets. Studies on mice that were deficient in class I HDAC members showed the significance of histone deacetylase (HDAC) enzymes in organisms. With severe proliferation problems and overall development retardation, HDAC1-null animals pass away prenatally; HDAC2-null mice pass away the day at the first after birth from cardiac deformities; and HDAC3-nulll mice pass away prenatally from disorders in gastrulation. HDACs appear to be crucial for the express of genes. It has stated several times that their levels change significantly depending on the kind of tumor and in cancer cells. Prostate, stomach, lung, esophageal, colon, and breast cancers all have significant levels of HDAC1 expression [2].

Chromatin
Found in eukaryotic cells is the combination of genomic DNA with proteins**.**
Each DNA molecule attached to a histones is referred to as a chromosome, and chromatin is made up of 147 base pairs of DNA wrapped around a proteins core known as a histone.

Structure of Chromatin
Numerous variables influence the chromatin structure. Phases of the cell cycle play a major role in determining the overall structure. They experience a number of structural alterations during cell division. During metaphase, when the DNA is duplicated and partitioned into two cells, the shape of the chromosomes changes and is readily apparent under a light microscope [3].The chromatin group goes through three stages: DNA is wrapped around histone proteins to create nucleosomes. The nucleosome is a 30 nm fiber made up of many histones.
The 30 nm fiber's higher-level DNA packing into the metaphase chromosome.

Functions of Chromatin include
1. Preventing DNA damage.
2. Tightly packing of the DNA to fit into the cell.
3. Control the DNA replication and gene expression.
4. Support the DNA molecule to permit the process of cell cycle – meiosis and mitosis [4].

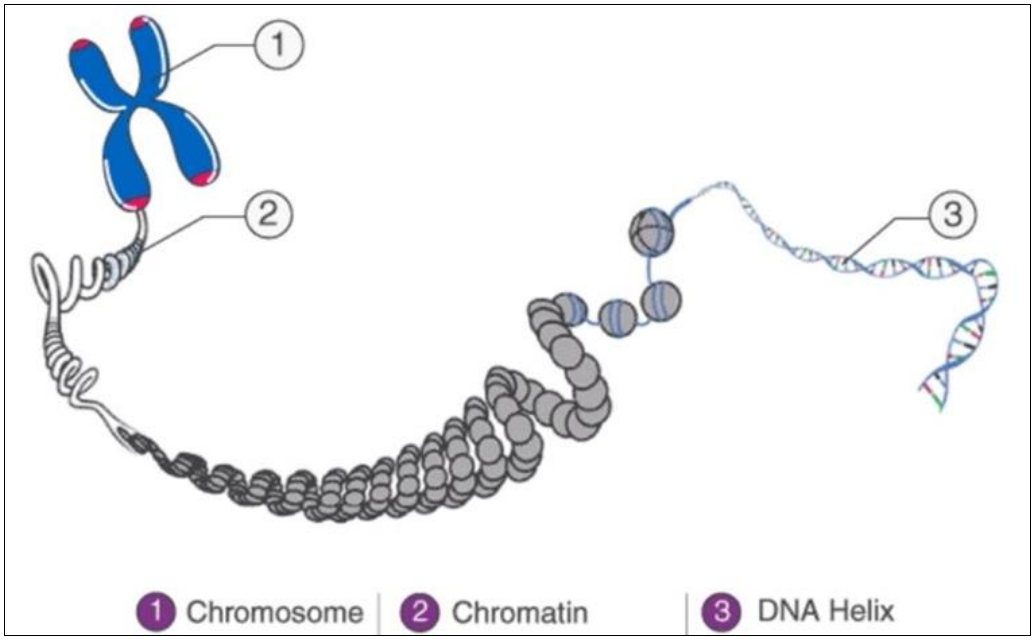


Fig 1: Structure of chromatin

Nucleosome

Is the fundamental building block of DNA pack in eukaryotes. A nucleosome is a structure that looks like thread spun around a spool and is made from of a piece of DNA wrapped around eight histone proteins. The core component of chromatin is the nucleosome. A histones octamer, which is an eight-protein group which are called histones surrounds a little less than two twists of DNA in each nucleosome. The histone proteins H2A, H2B, H3, and H4 each make up two copies of the histone octamer [5].

Function of Nucleosome

1. It organizes around 200 bp of DNA at the first stage of genomic compaction [11].
2. By offering a framework for binding of chromatin enzymes and presenting a combinatorial array of post translational alterations, the nucleosome serves as a signaling center for chromatin-templated activities (PTMs).
3. Further genome compacting is possible because of the nucleosome's capacity to self-assemble into higher-order chromatin structure.

Protein interactions within the nucleosome

The "histones fold," a distinctive structure pattern seen in the core histones proteins, is composed of three alpha-helices (1-3)) separated by two loops (L1-2). The histones create H2A-H2B heterodimers and H3-H4 heterotetramerss in solution. In the cases of histones H3 and H4, two of these dimer a 4-helix bundle that is stabilize by strong H3-H3' contact. Histones dimerizes about their long 2 helices in an anti-parallel orientation [6]. Due to inter interactions between H44 and H2B, which entail the creation of a hydrophobic cluster, the H2A/H2Bb dimer attaches to the H3/H4 tetramer. A core H3/H4 tetramer is sandwiche between two H2A/H2B dimers to produce the histone octamer. The histone octamer is only stable in the presence of DNA or at extremely high salt concentrations because all four core histones have a strongly basic charge [7].

Histone - DNA interactions

Over 120 directed protein-DNA interaction as well as several hundred water mediated ones may be found on the nucleosome. Direct protein-DNA interactions are not equally distributed throughout the surface of the octamer, but rather are concentrated at specific places. These result from the development of two different types of DNA binding site in the octamer, the L1L2 site and the 11 site, which utilise the 1 helix from two nearby histones. The majority of interactions with the DNA are formed through salt linkages and hydrogen bonds between side-chain basic and hydroxyl groups, main-chain amides, and the phosphates in the DNA backbone. This is significant because nucleosome distribution throughout genomes necessitates the existence of a non-sequence-specific DNA-binding factors. Despite the fact that nucleosomes seem to favor some DNA sequences over others [8].

Histone modification

Histone acetylation

Is a significant epigenetics alteration that modifies the structure of chromatin and controls the expression of genes by open or shutting the chromatin structures. It is crucial for the progression and differentiation of the cell cycle [16].An acetyl group is added to lysine residues in the protrude histones tail during the process of histone

acetylation. Histone acetyl transferees (HATs), which add acetyl groups to histones, and histone deacetylase (HDACs), which remove them, regulate it in a manner that is often related with transcriptional activity. [9].

Histone acetyl-transferees classification

HATs are categorized into two types: type A and type B
Type A are nuclear HATss
Type B are cytoplasmic HATss.
Type A HATs are further divided into five families: GNAT family, p300/CBP family, MYST family, basal TF family, and NRCF family.
Type B HATss are divided into HAT1, HAT2, HatB3.11, Rttt109, and HAT4 [10].

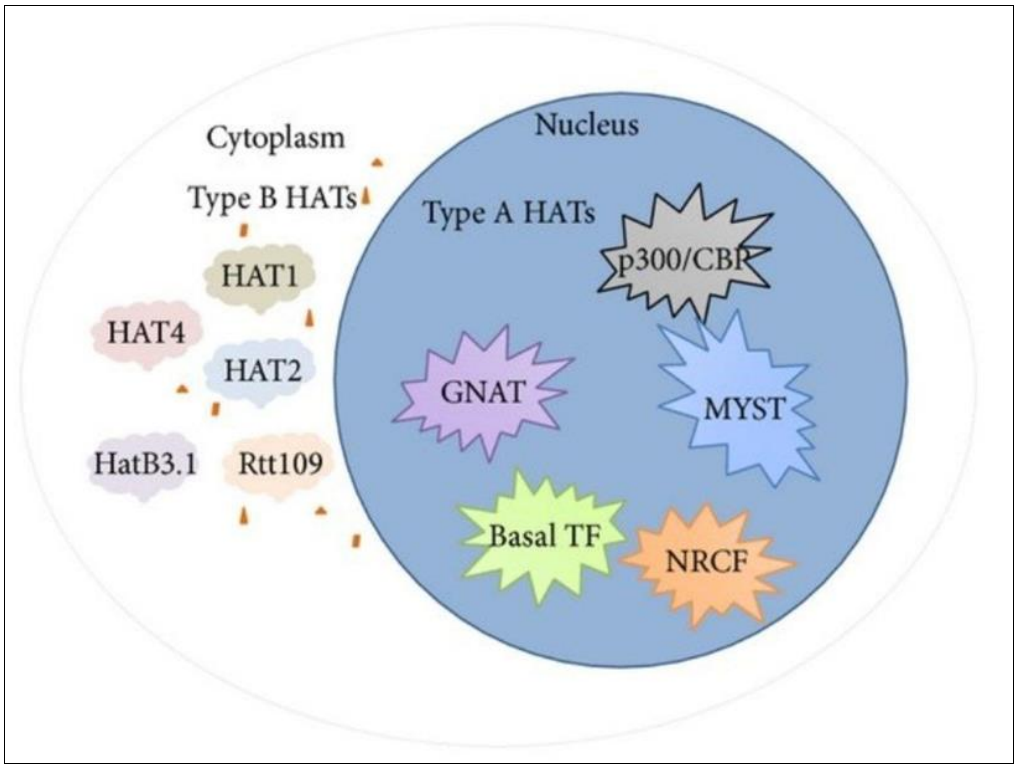


Fig 2: Histone acetyl-transferases classifications

Histone deacetylase

Is a major epigenetic modification that alters the chromatin structure and regulates gene express by open or closing the chromatin structure. It is essential for the cell cycle's progression and differentiation
The process of histone acetylation involves the added of an acetylation group to lysine residues in the projectings histone tails. It is regulated in a way that is frequently connected to transcriptional activity by histone acetyl transferases (HATs), which add acetyl groups to histone, and histone deacetylasese (HDACs), which remove it them. I class (HDAC 1, 2, 3, and 8) Classs II (HDAC 4, 5, 6, 7, 9 and 10)
Class I, Class II, Class III (SIRT 1, 2, 3, 4, 5, 6, and 7) and Class IV (HDAC 11) HDACs are Zn2+-dependents enzymes with similar functional mechanisms. However, Class III HDACs are NAD+-dependent. Class I HDACs are express in all tissues. HDACs 1 and 2 have been associated with cellular function including proliferation and death, whereas HDAC3 is associated with the DNA damaged response. HDACs 4, 5, 7, and 9 are associated in cell differentiation and growth. HDAC11 regulates the production of interleukins, whereas sirtuins are crucial for DNA repair and cellular metabolism. Carcinogenesis and cancer are usually associated with HDAC dysregulation. The FDA has now authorized many HDAC inhibitors as anticancer drugs [11].

Epigenetic therapy

Is used of medication or other methods that affect the epigenome to cure disease. Epigenetic pathways have an impact on the development of many diseases, include cancer, heart disease, diabetes, and mental problems.
The study of changes in gene expression that do not come from changes in the DNA sequence is known as epigenetics. A variety of regulatory systems, including those that control DNA and chromatin, can change, leading to altered gene expression patterns. Although the genetic component of many diseases is well established, more research is continuously being done on the processes underlying many different ailments. It is well recognized that a large variety of illnesses alter the way that genes are expressed inside the body, and epigeneticc involvement is a likely theory for how this occurs. The symptoms of the illness may be brought on by these changes. A number of illnesses, including cancer, have been suspected of selectively activating or inactivating genes, allowing the tumorous tissues to evade the host's immunological response [12].

Three categories are commonly used to group together known epigenetic processes. The first is DNA methylation, which involves the methylation of a cytosine residue followed by a guanine residue (CpG) [13]. The majority of the time, DNA methylation draws proteins that fold that region of the chromatin and inhibit the associated genes. Histone alterations comprise the second group. Histones are proteins that aid in the compacting and folding of chromatin. Histones may be chemically altered in several ways and come in a variety of distinct forms. Gene expression is linked to contacts between histones and DNA, which are normally weaker as a result of acetylation of histone tails. Although histones can be chemically changed in a wide variety of places, the exact specifics of the histone code are now unclear. Regulatory RNA is the last class of epigenetic mechanisms [14].

Classes HDAC enzyme

HDAC inhibitors

Inducing cell death, apoptosis, and cell cycle arrest in cancer cells is one of the main functions of the relatively new family of anti-cancer drugs known as histone deacetylase (HDAC) inhibitors. The FDA has approved two HDAC inhibitors, vorinostat and depsipetide, following the clinical validation of their usage in cancer patients. Additionally, several HDAC inhibitors are now undergoing clinical trials for use as anticancer medications (either alone or in conjunction with also other anti-cancer treatments) [15].

Table 1: showing classes HDAC enzyme.

Zn^{2+}-dependent		NAD^{+}-dependent
Class I	Class IIa	
HDAC1	HDAC4	Class III
HDAC2	HDAC5	SIRT1
HDAC3	HDAC7	SIRT2
HDAC8	HDAC9	SIRT3
		SIRT4
Class IV	Class IIb	SIRT5
HDAC11	HDAC6	SIRT6
	HDAC10	SIRT7

HDAC inhibitors classification

HDAC inhibitors may be divided into five main chemical groups: I hydroxamic acids (hydroxamates), II short chain fatted acids (aliphatic), III Benz amides, IV cyclic tetra peptides, and V sirtuin inhibitors, include the pan-inhibitor as general Nicotinamide and the particular SIRT1 and SIRT2 inhibitors sirtino (for overview, see [28] and Table 1). (I) although trichostatin A (TSA), an HDAC inhibitor, has been approved by the FDA for the treatment of recurrent and refractory cutaneous T-cell lymphoma, vorinostat (suberoylanilide hydroxamic acid, SAHA), the first HDAC inhibitor, has not, is poisonous and is only used in laboratory trials (CTCL). The pan-HDAC inhibitors include belinostat (PXD-101), which is approved for the treatment of peripheral T cell lymphoma (PTCL), panobinostat (LBH589), which is approved for the treatment of multiple myeloma, and the drugs recently tested in clinical studies, such as givinostat (ITF2357), resminostatt (4SC201), abexinostatt (PCI24781), and quisin All three practinostatt (SB939), a medication that inhibits all three of the common HDAC subclasses (I, II, and IV), and CHR-3996, a medication that is a selective inhibitor of class I, are selective HDAC inhibitor in the family of hydroxamic acid that are being researched in people. Butyric acid and valproic acid (VPA), and phenylbutyric acid, respectively, are all acknowledged as being weak inhibitor of HDAC classes I and IIa. Along with other short chain fatted acid HDAC as inhibitors, VPA is now being tested in clinical trials as an anticancer drug in addition to being accepted for the treatment of migraines, bipolar disorder, and epilepsy [16]. (III) The three benzamides entinostate (MS-275-SNDX-275), tacedinaline (CI994), and 4SC2022, which are currently being assessed in clinical research, block the class I HDACs.

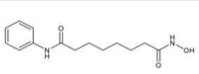
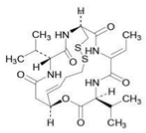
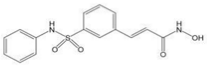
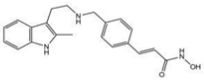
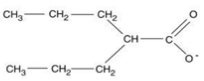
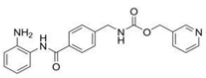
Table 2: Overview of selected histone deacetylases (HDAC) inhibitors.

Class	HDAC Inhibitor	Target HDAC Class	Clinical Status
hydroxamic acids	Trichostatin A	pan	preclinical
	SAHA	pan	approved for cutaneous T-cell lymphoma
	Belinostat	pan	approved for peripheral T-cell lymphoma
	Panabiostat	pan	approved for multiple myeloma
	Givinostat	pan	phase II clinical trials—relapsed leukemia and multiple myeloma
	Resminostat	pan	phase I and II clinical trials—hepatocellular carcinoma
	Abexinostat	pan	phase II clinical trial—B-cell lymphoma
	Quisinostat	pan	phase I clinical trial—multiple myeloma
	Rocilinostat	II	phase I clinical trial—multiple myeloma
	Practinostat	I, II and IV	phase II clinical trial—prostate cancer
	CHR-3996	I	phase I clinical trial—advanced/metastatic solid tumors refractory to standard therapy
short chain fatty acids	Valproic acid	I, IIa	approved for epilepsia, bipolar disorders and migraine, phase II clinical trials—several studies
	Butyric acid	I, II	phase II clinical trials—several studies
	Phenylbutyric acid	I, II	phase I clinical trials—several studies
benzamides	Entinostat	I	phase II clinical trials—breast cancer, Hodgkin´s lymphoma, non-small cell lung cancer, phase III clinical trial—hormone receptor positive breast cancer
	Tacedinaline	I	phase III clinical trial—non-small cell lung cancer and pancreatic cancer
	4SC202	I	phase I clinical trial—advanced hematological malignancies
	Mocetinostat	I, IV	phase II clinical trials—Hodgkin´s lymphoma
cyclic tetrapeptides	Romidepsin	I	approved for cutaneous T-cell lymphoma
sirtuins inhibitors	Nicotinamide	all class III	phase III clinical trial—laryngeal cancer
	Sirtinol	SIRT 1 and 2	Preclinical
	Cambinol	SIRT 1 and 2	Preclinical
	EX-527	SIRT 1 and 2	cancer preclinical, phase I and II clinical trials—Huntington disease, glaucoma

Approval HDAC inhibitors

Four HDAC inhibitors for anti-cancer medications have so far received approval from the US Foods and Drugs Administrations (US FDA): Vorinostat, Romidepsin, Belinostat, and Panobinostat (Table 1). More than five HDAC inhibitors, including repositioning of HDAC inhibitors that have previously received approval, are also undergoing clinical trials in phase III.

Table 3: Approval HDAC inhibitors

Tradename	Chemical names	FDA approved indication	Classification	Structure	Clincal trials
Zolinza®	Vorinostat SAHA	CTCL	Hydroxamate		Multiple myeloma Mesothelioma Neuroblastoma Glioblastoma Non-Hodgkin lymphoma
Istodax®	Romidepsin FK228	CTCL PTCL	Cyclicpeptide		Multiple myeloma Breast cancer Lymphoma Sarcoma Small cell lung cancer
Beleodaq®	belinostat, PXD101	Multiple melanoma	Hydroxamate		CUP Ovarian cancer Hepatocarcinoma Soft tissue sarcoma NSCLC AML and MDS
Farydak®	Panobinostat LBH-589	CTCL	Hydroxamate		Multiple myeloma CML Hodgkin's lymphoma Metastatic melanoma Prostat cancer
Depacon®	Valproic acid	Epilepsy Seizures Bipolar disorder Migraine	Carboxylate		Cervical cancer Ovarian cancer Breast cancer AML and MDS Spinal muscular atrophy
On trial	Entinostat MS-275		Benzamide		Hormone receptor-positive advanced breast cancer Breast cancer Hodgkin's lymphoma NSCLC Colorectal cancer

Application of HDAC inhibitors

In treatment of cancer

A novel family of cytostatic drugs called histone deacetylase inhibitors prevents the growth of tumor cells both *in vitro* and *in vivo* by causing cell cycle arrest, differentiation, and/or death [17]. Histone deacetylase inhibitors work against tumors by altering the expression of oncogenes or tumor suppressor genes, via adjusting how histones and/or non-histone proteins, such transcription factors, are acetylated and deactylated. Histone acetylation and deacetylation are crucial processes in the control of gene transcription and chromatin architecture. An example of a therapy that is effective for Beleodaq is a histone deacetylase inhibitor prescribed for patients with relapsed or unresponsive peripheral T-cell lymphoma (PTCL). Based on the rate of tumor response and the length of the response, this indication is authorized under rapid approval [18].

Fig 3

The role of HDAC in treatment diabetes

Histone deacetylase played a growing important role in the prevent and treatment of a variety of metabolise diseases and malignancies. This review emphasizes their complex function in diabetes mellitus and its related consequences. Key conclusions: The involvement of numerous epigenetic markers in the management of diabetes mellitus has been established by recent studies and publications. The HDAC enzyme controls chromatin structure and transcripts genes in the nucleus that produce different proteins that govern bodily metabolic processes. It primarily affects gene expression by removing an acetyl group from its precursor's proteins and controlling the metabolic enzymes acetylation in mitochondrial and cytoplasm [35]. The current study concentrates on the intrinsic function of HDAC inhibitors as a newly discovered treatment for diabetes and its

consequences, revealing their utility in avoiding insulin resistance, cell death, and protections against cytokines mediated assault on pancreatic cells [19].

HDAC in viral diseases

Numerous viruses are controlled in their reproduction by HDACs (Table 4). Here, we'll go through the role [37].

Table 4: The role of HDACs in viral infections

Virus	HDAC	Molecular mechanism	Clinical effect	References
DNA viruses				
HBV	HDAC1, 2	HBx forms a multiprotein complex HDAC1/2, MTA1, HIF-1	Angiogenesis and metastasis of HBV-associated HCC	Semenza 2004; Yoo et al. 2008
HCMV	HDAC3	HDAC3 represses the HCMV MIEP	Repression of viral replication	Meier 2001; Murphy et al. 2002
HSV-1	HDAC1	HDAC represses viral transcription during latency via HCF-1. ICP0 inhibits the HDAC1/CoREST complex and favor the HSV reactivation	Control of HSV-1 latency and reactivation in neurons	Wysocka et al. 2003, Everett et al. 2009
EBV	HDAC1, 2, 7	Histone deacetylation in response to phosphorylated MEF-2D transcription factor. HDAC7 represses the Zp promoter. HDAC1/2 represses the TRF2 promoter binding	Control of EBV latency	Gruffat et al. 2002; Bryant and Farrell 2002; Zhou et al. 2009
HPV	HDAC1	E7 viral oncoprotein disrupts the Rb/E2F/HDAC1 repressor complexes and favors cdc25A transcription. E7 binds HDAC and favor E2F2 transcription in keratinocytes. E7 recruits HDAC and blocks the IRF-1 transactivation function, a tumor suppressor	E7 HPV favors carcinogenesis through binding to cellular factors involved in cell cycle regulation and differentiation	Nguyen et al. 2002; Longworth & Laimins 2004; Park et al. 2000
RNA viruses				
HCV	HDAC	HDAC favors the expression of HIF, a hepcidin regulator	HCV-induced oxidative stress suppresses hepcidin expression	Miura et al. 2008
HIV	HDAC class I & class II & class III	HDAC represses the HIV-1 LTR transcription through the formation of inhibitory complexes including HDACs and several transcription factors and repressor proteins. HIV-1 virion-associated HDAC1 could favor early post-entry events. SIRT1 regulates HIV transcription via Tat deacetylation	Formation of HIV cellular reservoirs in both myeloid and lymphoid cells resulting in viral persistence	Van Lint et al. 1996, Coull et al. 2000, Williams et al. 2006, Marban et al. 2005, Marban et al. 2007, Rohr et al. 2003; Reuse et al. 2009; Imai & Okamoto 2006; Jiang et al. 2007; Sorin et al. 2009; Pagans et al. 2005; Kwon et al. 2008; Zhang et al. 2009
RSV	HDAC1	HDAC1 associates with STAT1 and Bcl-3 on the IL-8 promoter	Decreased IL-8 production during airway inflammation to favor RSV replication	Jamaluddin et al. 2005

Histone deacetylase inhibitors for cardiovascular conditions

Histone deacetylase inhibitors (HDACi) use epigenetic processes to control gene expression. A growing body of research indicates that HDACi work through epigenetic processes to have antiproliferative, antioxidant, antineoplastic, and proapoptotic effects.

Effects on select cardiovascular conditions

Arterial pressure is high. HDACi have also been investigated in the setting of atrial fibrillation, a potentially fatal and crippling disease that raises the chance of death by stroke, dementia, and other causes. Additionally, it has been demonstrated that inhibiting histone deacetylase can lower the duration of fibrillate, atrial fibrosis, intra atrial adipocytes, and immune cell infiltration in mice without compromising heart function or reversing atrial fibrosis or atrial arrhythmias [20].

Stroke. Atherosclerosis and infarction: Valproic acid decreased infarct size by 50% in a rat model of myocardial infarction, retained systolic function following acute myocardial infarction, and enhanced cardiac perfusion. Epigenetic control of stress-related inflammation and fibroblast activation in the heart can cause or make heart failure worse [21]. Valproic acid treatment reduced proinflammatory and fibrotic responses in a number of experimental animals.

Which HDACi should be used?

Trapoxin A is one example of an HDACi that has limited therapeutic use due to its low *in vivo* bioavailabilityy and hazardous side effects at high doges also, like butyrate and phenylbutyratee, breakdown quickly when administered intravenously. Numerous additional substances have been employed as effective HDACi in the treatment of cancer [22]. Many of these substances also inhibit protein phosphorylation, protein methylation, and DNA methylation in addition to being general HDAC inhibitors. The well-known and generally well-tolerated medication valproic acid, on the other hand, is a class1 I (and, to a lesser degree, class II) histones deacetylase inhibitor. In addition, valproic acid may have a reduced risk of QT prolongation than other HDACii [23].

Histone deacetylase inhibitors for neurodegenerative disorders

A diverse collection of ailments known as neurodegenerative diseases are more common as the population ages. These conditions are characterize by progressive damage to the brain and spinal cord, which slowly erodes the capacity of the central or peripheral neurological systems to carry out simple activities like thinking and remembering. Alzheimer dementia (AD), Parkinson diseases (PD), Huntington diseases (HD), amyotrophic

lateral sclerosis (ALS), spinal muscular atrophy (SMA), and Friedrich ataxia are the most prevalent neurodegenerative illnesses (FRDA). The biochemical and molecular mechanisms involved in the etiology of neurological illnesses have been the subject of extensive investigation in experimental animals, but the related therapeutic treatment methods have not been successful in halting the progression of deficits [24].

The fifth largest cause of mortality for those 65 years of age and beyond is Alzheimer's disease (AD), the most prevalent neurodegenerative condition among the elderly. About 80% of instances of dementia that develop over time due to memory loss and cognitive decline brought on by neuronal malfunction and ultimately neuronal death are caused by the illness [25].

One of the most prevalent neurodegenerative brains illnesses is Parkinson diseases (PD) [47]. 2% of the population over the age of 65 are affected.

Progressive chorea, motor dysfunction, cognitive deficits, and behavioral problems are all symptoms of Huntington diseases (HD), an autosomal dominant hereditary neurodegenerative illness [26].

Lower and uppers motor neurons are the primary targets of the deadly neurodegenerative condition known as amyotrophic lateral sclerosis (ALS). Within 2–5 years of diagnosis, motor neuron degeneration results in gradual muscular atrophy, paralysis, and death [27].

Spinal muscular atrophy (SMA) is a degenerative illness with a juvenile origin that causes the selective loss of motor neurons in the spinal cord and causes the muscles of the limbs and trunk to atrophy [28]. One of the top hereditary causes of infant mortality worldwide is SMA.

HDAC's capacity to successfully pass the blood-brain barrier (BBB) and enter the central nervous system additionally, it should be noted that HDAC inhibitors are frequently given systematic (e.g. intraperitoneally or oral). Unwanted side effects from such therapies might affect the entire body in addition to the target area. A more careful assessment of HDAC's cytotoxic profile is necessary [29].

Histones deacetylase (HDAC) inhibitors in treated of diseases chronicles' compare with different synthetic and natural heterocyclic compound for study different biological activity like tetrazine, ox diazole, piperine, harmalole etc [30, 50].

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