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Role of Histone Deacetylase Inhibitors on Viral Replication: A Review

Supriyo Saha [1,*], Dilipkumar Pal [2]

[1] Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Premnagar, Dehradun, Uttarakhand-248007, India; supriyo9@gmail.com(S.S.);
[2] Department of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, C.G., 495 009, India;drdilip2003@yahoo.co.in(D.P.);
* Correspondence: supriyo9@gmail.com(S.S.);

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Abstract: Established antiviral agents fail to prove their existence to kill constantly mutated viruses. Previous work suggested that HDAC enzymes interfere with the host immune system and stop the initiation and replication of the virus. In this manuscript, we have tried to establish the relationship between HDAC enzymes and different viral infections. As well as portray a detailed study on the role of HDAC inhibitors (HDACI) as an antiviral agent. As per the study, we came to know that HDAC 1, 2, 3, 6, and 8 enzymes are associated with viral replications. Scientists explored the relationship between HDAC enzyme and the progression of HIV, hepatitis-B/C, herpes simplex, influenza, and other respiratory viruses. Among all the established and synthesized HDAC inhibitors, SAHA, trichostatin-A, vorinostat, panobinostat, entinostat, and RGFP966 showed good activity. As per structural features, quinolone, indole, thiazole, benzimidazole, and pyrazole heterocyclic groups showed remarkable results. So, HDAC inhibitors effectively conquer different viral replication.

Keywords: HDACI; HIV; HCV; HSV;influenza virus; RSV.
Abbreviations: HDAC: Histone deacetylase; HDACI: Histone deacetylase inhibitor; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; HSV: Herpes simplex virus; HBV: Hepatitis B virus; DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; CD4: Cluster of differentiation 4; CD8: Cluster of differentiation 8; RSV: Respiratory Syncytial Virus;.

1. Introduction

Famous virologist Stephen Morseby said that almost twenty different viruses exist in nature for vertebrates [1]. As per the viral database, fifteen viral families such as Adenoviridae, Papillomaviridae, Herpesviridae, Baculoviridae, Poxviridae, Parvoviridae, Retroviridae, Reoviridae, Picornaviridae, Flaviviridae, Caliciviridae, Coronaviridae, Bunyaviridae, Orthomyxoviridae and Paramyxoviridae were established till date [2]. Among them, poxvirus, herpes, adenovirus, papillomavirus and influenza, poliovirus, retrovirus, and arenavirus are associated with DNA and RNA virus categories, respectively [3]. In immune-compromised patients, antiviral drug resistance is one of the main concerns. Resistance toward anti-HCV drugs was observed due to inadequate proofreading of RNA polymerase and genetic diversity [4]. Antigenic shift-drift and latency regulated the mutation and drug resistivity towards influenza and herpes viruses [5]. In treating viral manifestation, antiviral drugs target nucleic

acid polymerase, protease, integrase, neuraminidase, DNA-dependent DNA/RNA polymerase, and RNA-dependent RNA polymerase enzymes [4, 5].

In spite of the presence of large repositories of antiviral targets, humans are still infected with the same [6, 7]. Climate change and global warming help the microbial entity to facilitate their growth and always be safe from the host's immune response [9]. Sometimes microbes utilize the host defense mechanism for their mutation (flu, influenza, etc.) [9-10]. So, in search of a new target for antiviral therapy, we focused on the versatility of the histone deacetylase (HDAC)enzyme. Then another question popped into our mind Why HDAC? [11, 12]Previous studies said that some classes of HDAC inhibitors effectively suppress the growth of viruses by interacting with the host defense mechanism [13, 14].

In this manuscript, we have tried to establish the relationship between HDAC enzymes and different viral infections. As well as portrayed the role of HDAC inhibitors (HDACI) on viral replications.

2. Types of HDAC Enzymes and Approved HDACI

There are four classes of HDAC enzymes such as class-I, II, III, and IV are exist. HDAC 1,2, 3, and 8 belong to class-I HDAC enzyme. HDAC 4, 5,6, 7, 9, and 10 fit into class II. HDAC11 belongs to class IV, and sirtuin 1-7 belongs to class-III HDAC enzyme [12, 13]. These enzymes are involved in the elimination of the acetyl group from lysine amino acid present in the terminal position of histone, which progressively silenced genetic expression via chromatin remodeling. There are69 HDAC inhibitors available in the PubChem database. Among them, 24 molecules belong to the quinolone nucleus, followed by benzamide, naphthalene, pyrrole, chromone, benzimidazole, pyrimidine/thienopyrimidino, benzsulfonamide, and cycloheptanyl pyrrole aniline cyclobutene, etc. as functional groups [14, 15].

3. Importance of HDACI in the Treatment of Viral Infections

3.1. Role of HDACI in the treatment of HIV infection.

Nowadays, treatment of HIV infection with antiretroviral drugs faces a big hurdle of dormant HIV-infected cells. These cells work as storage of dormant HIV infection which may be chronic or asymptomatic but still capable of transfecting other people. Sometimes, the carrier does not even know about this fact of carrying dormant infection cells because dormant cells slowly grow for a huge period during therapy. Still, in the last lap, a progressive increase in viral load was observed. Simultaneously the defense mechanism deteriorates due to low $CD4^+$ cell count and HIV infection overdue the immune system [19]. In this situation, the annihilation of latent HIV infection reservoirs is the most important step in treating HIV patients. The latent HIV resided well in the resting $CD4^+$-T cells in a stable form, and observed that $CD4^+$-T cells contained HIV-1 DNA. The anti-HIV treatment module requires a lot of time to fully destroy the latent reservoir and germs of HIV infection well situated within the reservoir for a lifetime [20]. There were some other processes for latency, such as chromatin remodeling, methylation in DNA structure, and change in transcriptional behavior. Chromatin remodeling is directly related to HIV infection and host cell chromosomal structure. Two types of chromatins directly impact HIV latency, such as euchromatin and heterochromatin. After transcription, the expressible part of the DNA structure is observed in euchromatin, and the non-expressible part is observed in the heterochromatin part. In the case of HIV latent

information reservoir, J-Lat, provirus of latent HIV infection, and centralized alphoid structures were observed in heterochromatin structure. Nucleosomes such as nuc0 and nuc1 were the two most important parts of chromatin structure, and collectively they form long terminal repeats of the HIV gene (well observed in proviral conditions also). Reverse latency was connected with the structure -of the nuc1 nucleosome [21]. The behavior of the nuc1 nucleosome is directly related to the acetylation of histone protein. Histone deacetylase enzyme was well situated within the long terminal repeat along with the nuc1 nucleosome. Among various types of histone deacetylase enzymes, HDAC-1well incorporated in HIV-1 long terminal repeat using different nuclear factors. Methylation in deoxyribonucleic acid structure strengthens the latency of the HIV-1 virus [22]. The latent structure of HIV-1 is directly linked with immortalized Jurkatcells and $CD4^+$ - T cells [23-24]. The host cell defense mechanism contained LEDGF/p75 host factor directly bound with integrase enzyme. These internal factors and latent HIV-1 genes are well represented within Jurkat and $CD4^+$-T cells [25].

3.1.1. Importance of Ethyl ketone-based HDAC inhibitors in the reactivation of latent HIV.

Yu *et al.* developed a series of ethyl ketone-based histone deacetylase inhibitors targeting HIV latency reversal. The background of the work was developed using the molecule **1 [**N-(2-aminophenyl-4-thiophenyl)-6-(2-oxo-1-oxa-3,8-diazaspiro[4.5]decan-8-yl)pyridine-3-carboxamide**]** and molecule **2[**2-(1-methylazetidine-3-carboxamide)-6-(2-methoxyquinoline)-Imidazolyl-nonan-7-one**]**followed by inhibitions of five types of histone deacetylase enzymes [HDAC 1, 2, 3, 6 and 8] and assessment of HIV latency reactivation in terms of cell survival analysis using 0.1% and 5.0% normal human sera addition into Jurkat cell. Outcomes showed that molecule **2** observed slightly better activity than molecule **1** in terms of latency removal. So, using the structural features of molecule **2**, a series of molecules were developed. In the new series, the 1-methylazetdine group was replaced with spiro compounds. In molecule **1**, the spiro compound was available in the structure, so the new series was developed using the structural importance of both molecules. Then the new series of molecules were evaluated against deacetylase enzymes and also with reactivation of the HIV latent reservoir. Results revealed that molecule **3 [**2-(1-methyl-1-azaspiro [2.5] octane -3-carboxamide)-6-(2-methoxyquinoline)-Imidazolyl-nonan-7-one] observed with maximum histone deacetylase enzymes inhibition (IC_{50} values = 0.19 nM [type=1], 1.4 nM [type=2], 0.19 [type=3], 157 nM [type =6] and 3379 Nm [type =8]) and reversal of HIV latency (EC_{50} values = 26 nM [with 0.1% normal human sera] and 83 nM [with 5.0% of normal human sera]). Molecule **3** was synthesized upon reaction between [2-(1-amino)-6-(2-methoxyquinoline)-Imidazolyl-nonan-7-one] and 6-(tert-butoxycarbonyl)-6-azaspiro [2.5]octane-1-carboxylic acid in presence of isopropylamine and other deblocking agents. Most HIV-infected virions are stored in the memory T cells in the dormant state, HDACI, and normal antiretroviral drugs collectively worked as lethal weapons to kill the source of HIV infection through the Shock and Kill strategy. After analyzing the structural features, we confirmed that introducing spiro compounds in the side chain of the imidazolyl side-chain enhanced the receptor interaction, histone deacetylase enzyme inhibitions, and efficient reversal of the HIV latent reservoir [26].

3.1.2. Panobinostat effectively reversed HIV latency in combination with antiretroviral therapy.

Tsai *et al.* experimentally proved the importance of established histone deacetylase inhibitor panobinostat (**4**) in managing HIV infection in combination with antiretroviral

therapy. At first, $CD4^+$-T cells were obtained from animals. By doing this, white blood cells of human and BLT mice (immune-deficient mice transplanted human blood cells), then these cells were incubated with various types of $CD4^+$-T cells, followed by being treated with panobinostat to measure the level of RNA induction.

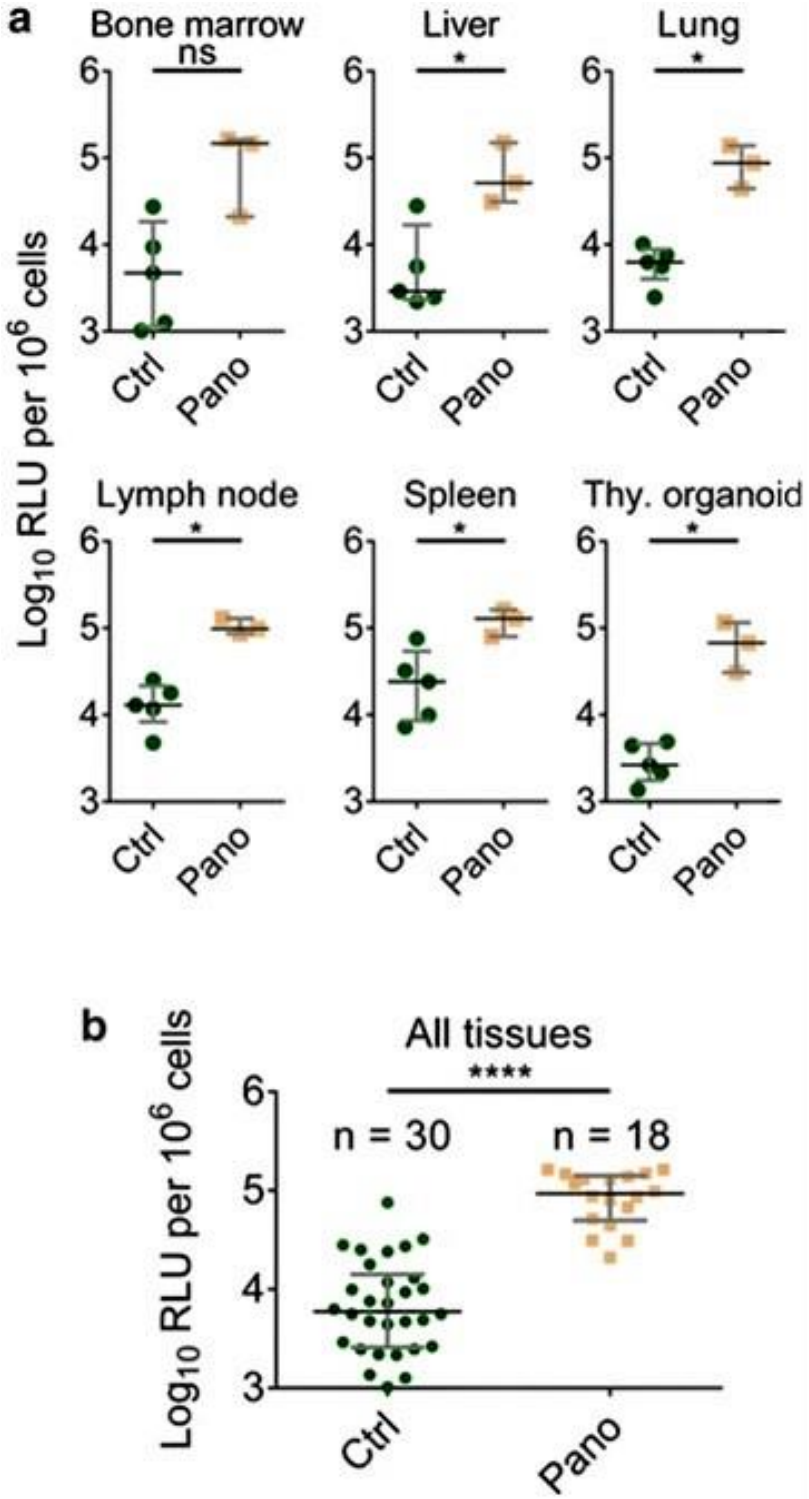

Figure 1. Role of Panobinostat on acetylation of histone protein [27].

Then quantitative viral outgrowth assay, resting cells were treated with efavirenz, abacavir, raltegravir, panobinostat, and phytohemagglutinin (plant protein responsible for heme agglutination). Then the researchers treated the peripheral blood mononuclear cells with panobinostat and acetylation of the H3 position of histone protein measured by flow cytometric

process. Then BLT mice were infected with HIV-1 infection. Data showed a 3.0-fold and 3.5-fold increase in histone H3 observed with 10 nM and 20 nM panobinostat treatment. Then the measurement of latency reversal was measured with 20 nMpanobinostat treated on patients suppressed with antiretroviral medications. Outcomes showed that three patients among ten to twelve patients observed 6.2, 3.7, and 3.2 folds increased HIV RNA levels. Viral outgrowth measurement data also showed that the number of HIV infectious cells/billion was 389 and 630 with untreated and panobinostat (20 nM) treated cells. To justify the *in-vitro* data, an *in-vivo* experiment to assess the level of histone acetylation was performed using 2 mg/Kg of panobinostat on bone marrow, liver, lung, lymph node, spleen, and thymic organoid; outcomes showed that most of the organs observed with a higher rate of histone acetylation almost 15.6-fold higher in panobinostat than untreated cells (Figure 1). These data collectively confirmed that panobinostat worked on treated mice without remarkable changes in the HIV infection and $CD4^+$-T cells associated with HIV-infected animals. So, we stated that panobinostat (10 nM and 20 nM) effectively reversed HIV latency [27].

3.1.3. Impact of HDAC1 on HIV replication.

Larguet *et al.* suggested that histone deacetylase-1 positively impacted the replication of HIV infection. HIV virions in the host cell interacted well with host cell protein and reversed transcripted complementary DNA structure well incorporated within the host chromosome, considered an essential factor for HIV growth. To understand the importance of histone deacetylase enzyme on HIV infection pattern, FLAG-HDAC1 plasmid, small interfering RNA, HIV-1 HXB2 integrase antisera, anti-HIV-1 integrase monoclonal antibody, and human embryonic kidney 293T cells were considered. In this way, the presence of HIV-1 viral integrase-linked protein was evaluated. As we know, two long terminal repeat sections (U5-U3 and MuLV) were present.

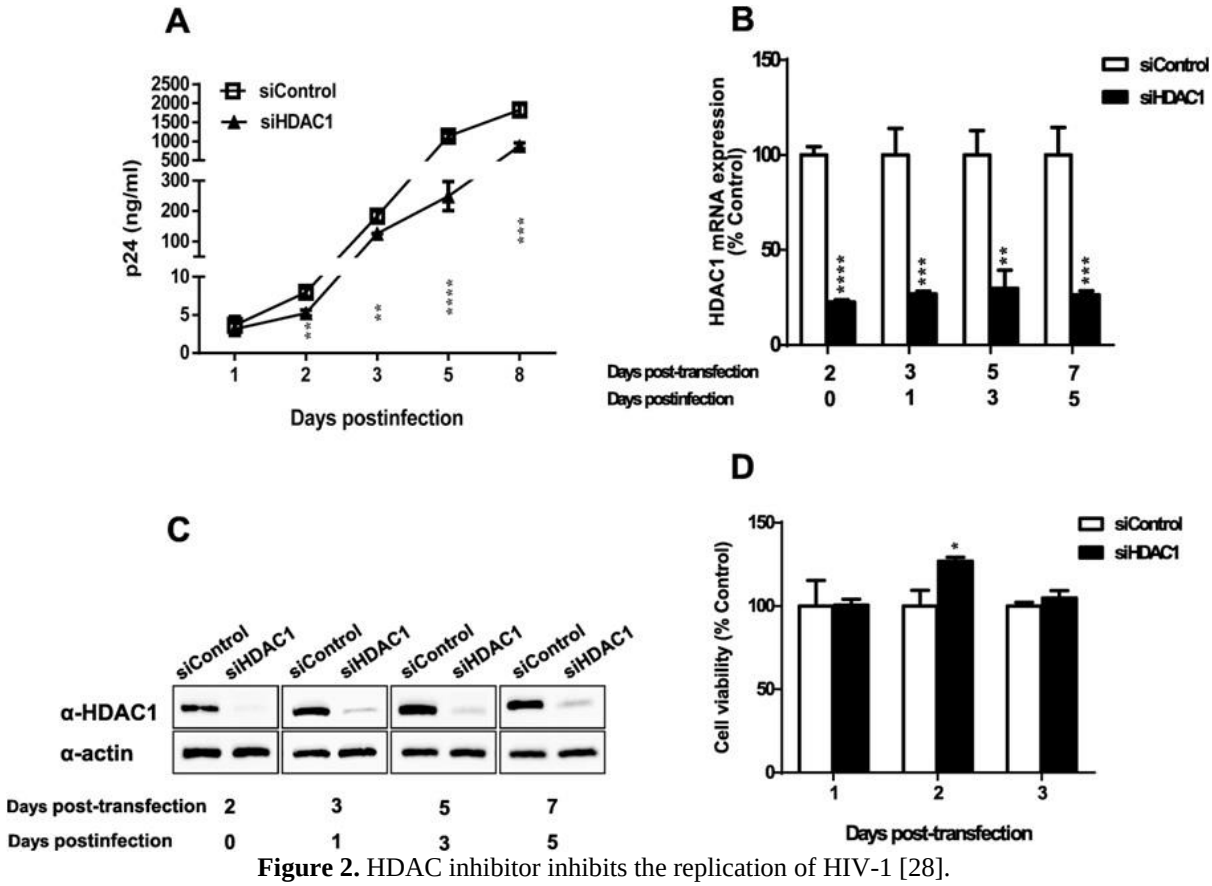

Figure 2. HDAC inhibitor inhibits the replication of HIV-1 [28].

In this assessment, a biotin-linked deoxyribonucleic acid present in the U3 section of the repeat terminal and the MuLV repeat terminal was fused with streptavidin (protein isolated from *Streptomyces avidinii*) expressed in embryonic kidney cells. Immunoblotting assay was performed in the presence of Flap structure-specific Endonuclease 1, DEAD-Box Helicase 5, DEAD-Box Helicase 17, and Histone Deacetylase1 antibodies. To identify the interaction between HDAC1 and HIV integrase enzyme, western blot analyses were performed using anti-FLAG and anti-Integrase in the presence of immunoglobulin-G as control (Ig-G). Analysis data showed that the host protein was well connected with the integrase enzyme without FLAG-HDAC1 plasmid structure. In the assessment of the correlation between lowering HDAC1 and inhibition of HIV-1 infection, HeLa-CD4 cells were used. Outcomes said that after a certain time, minimization of HDAC1 leads to 4.5 times inhibition of HIV-1 infection and also a prominent increase in the percent p24 viral protein (Figure 2). Also, the small interfering HDAC1 amount was significantly lowered in integrated viral DNA load, directly correlated with HIV-1 late reverse transcription after quietening HDAC1 presence. These data scientifically confirmed that the histone deacetylase-1 enzyme regulated the infection pattern of HIV [28].

3.1.4. Histone deacetylase inhibitor with bryostatin derivative in the reversal of latent HIV.

Latency-activating agents are an important factor in the reversal of latent HIV infection. In this work, Brice *et al.* considered SDL-148 (largazole), JMF 1080, SDL-256, and vorinostat as histone deacetylase inhibitors and bryostatin-1, SUW133, and SUW124 as protein kinase C modulators. Then fluorescence-activated cell sorting assay with green fluorescent protein data was performed using JLAT cells to identify which histone deacetylase inhibitor effectively reversed HIV latency at toxicity value. After one day of incubation with histone deacetylase inhibitors (concentration: 10 µM, 1.0 µM, and 0.1 µM) and considering tumor necrosis factor-alpha, and vorinostat as positive control molecules, we observed that largazole (**5**) was highly efficient as latency activating agent as compared to vorinostat. And at 100 nM concentration, SDL-148 was the best molecule to induce the reactivating process. The researcher performed a cell toxicity study using the (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium) assay method, which showed toxicity profiles of all the histone deacetylase inhibitors was more or less similar to suberoylanilide hydroxamic acid (**6**) (Figure 3). Then bioluminescence assay was performed using luciferase enzyme with SDL-148 and JMF 1080; outcomes revealed that both the molecules observed good activity, whereas SDL-148 showed almost the same activity but tenfold lower concentration than suberoylanilide hydroxamic acid as well as largazole molecule efficiently acetylated the H3 position of histone protein but not acetylated the tubulin molecule, so we can conclude that largazole participated in chromatin remodeling also. Histone deacetylase inhibitors and protein kinase C modulators are synergistically worked on HIV latency; using the knowledge, we observed that bryologs are effectively complexed with largazole to inhibit latent HIV infection. So, these data confirmed the role of largazole and bryology in combination to activate latent HIV virions [29].

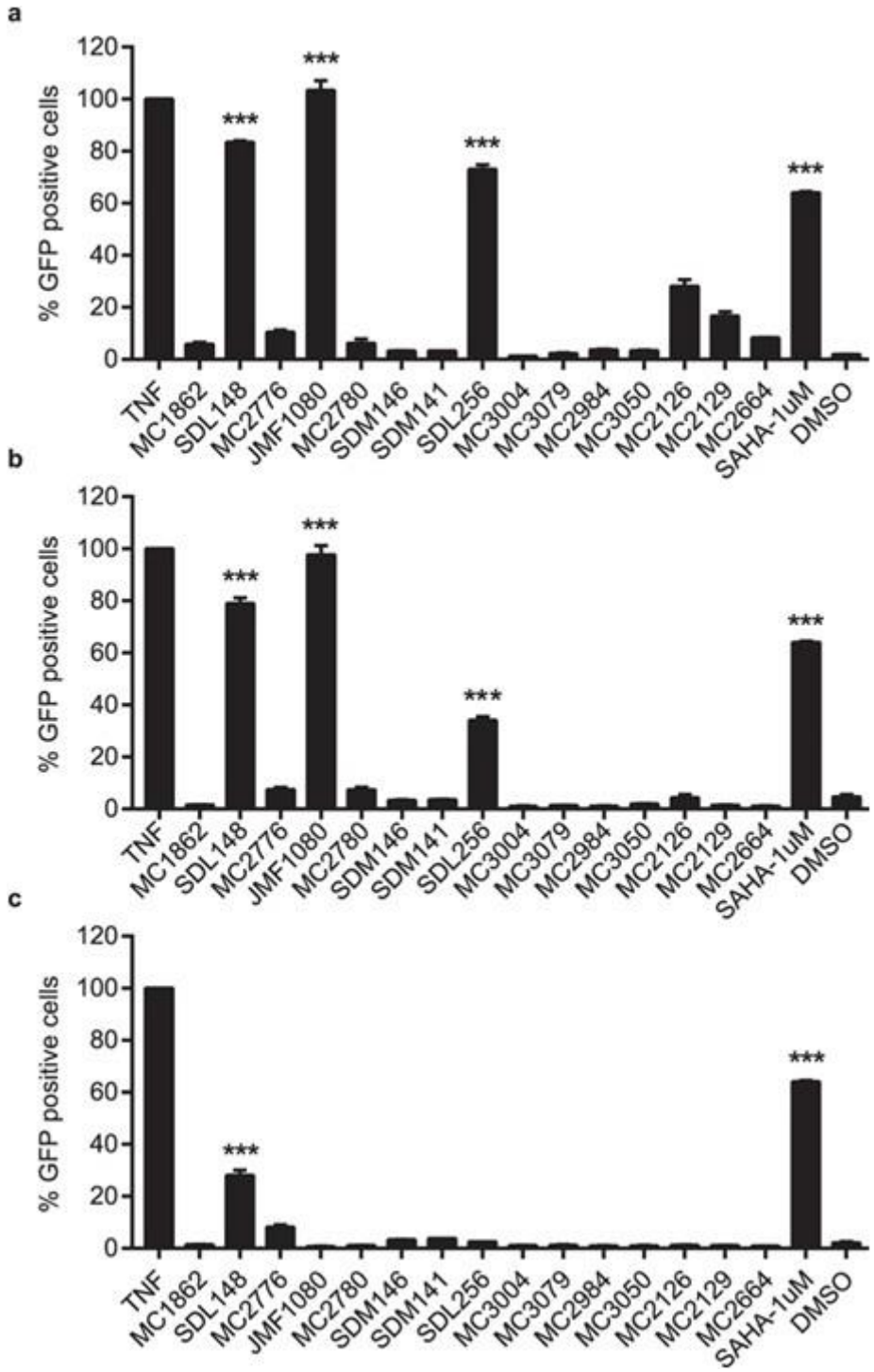

Figure 3. Role of largozole and Vorinostat on HIv-1 latency **[**29**]**.

In a similar research, Zaikos *et al.* stated that selective class-I histone deacetylase inhibitors combined with protein kinase C modulator showed better activity than pan-histone deacetylase-protein kinase C modulator combination because the first combination retained proviral response. In this research, enhanced green fluorescent protein data, viable cell count, downregulation of MHC-I protein depending upon HIV Nef protein, and percent HIV mRNA present in supernatant solution were used to establish the role of this combination therapy on the regulation of latent behavior of HIV infection. Outcomes revealed that class-I histone deacetylase inhibitor entinostat (**7**), in combination with protein kinase C modulator bryostatin-1 (**8**), effectively killsHIV-reactivated latent virions responsible for the reversal of infection [30, 31]. As we know, the retrovirus Gag protein is positively related to HIV-1 ribonucleic acid

formation, but overexpression of this protein reduces the formation of HIV-1 virion [32].In another research, Archin *et al.* suggested that vorinostat effectively removed the latent HIV reservoir. In this work, $CD4^+$-T cells were isolated from antiretroviral suppressed therapy patients and evaluated the HIV Gag ribonucleic acid level followed by treatment with vorinostat (335 nM), phytohemagglutinin (3.0 µg/ml) and interleukin-2 (60 Unit/ml). Outcomes revealed that up to 6 hr of treatment, vorinostat, and phytohemagglutinin (**9**) showed similar HIV ribonucleic acid expression, but after 6 h and up to 12 hr, only phytohemagglutinin showed this activity. As well as it confirmed that vorinostat (244 ng/ml) increased acetylation at the H3 position of histone protein by 1.6 times. These data confirmed the histone deacetylase inhibitor effectively reversed HIV latent information [33].

3.1.5. HIV-1 infection and HDAC6.

In most cases, class-I histone deacetylase inhibitors effectively worked in the reversal of latent HIV infection. But Valenzuela-Fernandez *et al.* reported the role of class-II histone deacetylase inhibitors (HDAC6) in managing HIV infection. As we know, two glycoproteins (gp40 and gp120) positively interacted with HIV virion. gp120 viral protein induced the acetylated alpha-tubulin associated in cellosaurus cell line (MT-2) infected with HDAC6. It was also observed that upregulation and downregulation of HDAC6 decreased and increased the progression of HIV infection, respectively. In this work, HDAC inhibitor trichostatin-A (**10**) increased the HIV-1 expression. This data stated the importance of histone deacetylase6 enzyme subtypes in treating HIV [34].

3.6. NCH-51 effective against latent HIV infection.

Victoriano *et al.* considered NCH-51 (structurally similar to suberoylanilide hydroxamic acid) histone deacetylase inhibitor in treating latent HIV infection.

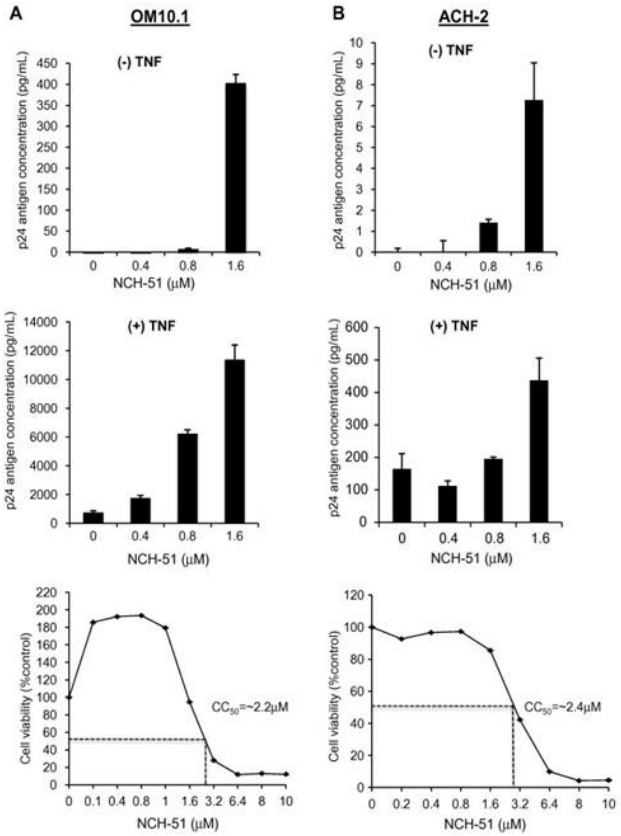

Figure 4. Importance of NCH-51 on latent HIV-1 [35]. © 2011 John Wiley and Sons.

In this work, myelomonocytic leukemia cell derivative (OM 10.1) and HIV-1 infected cell line (ACH-2) were considered to quantify the effect of NCH-47 (**11**), NCH-51 (**12**), suberoylanilide hydroxamic acid, trichostatin-A, and sodium butyrate in the formation of HIV-1 antigen related to the reversal of HIV infection, which showed that NCH-51 with maximum level of p24 antigen concentration; then to confirm the activity of NCH-51 on HIV-1 infection, both the cells were treated with different concentrations of NCH-51 (0.0, 0.4, 0.8 and 1.6 micromolar concentrations) followed by 1ng/ml of tumor necrosis factor-alpha outcomes showed that OM 10.1 cells observed with a higher number of p24 antigen as compare to ACH-2 cells and cell toxicity assessment data confirmed that NCH-51 was less toxic in both cells (cell toxicity concentration$_{50}$ = 2.2 micromolar and 2.4 micromolar, respectively) (Figure 4). These data confirmed that NCH-51 effectively activates the latency of the HIV-1 virus [35].

3.2. Role of HDACI on hepatitis.

Inflammation of the liver is mentioned as hepatitis, which has six types such as hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E, and hepatitis G. Hepatitis A is a very rare blood-oriented infection occurred due to the consumption of contaminated food and water. Hepatitis B is the most severe hepatitis linked with a severely damaged liver. In hepatitis C, most of the liver was affected, and the condition became worse as time proceeded. Both hepatitis B and C are transfected to patients by infected blood products. Hepatitis D is similar to hepatitis B, and hepatitis G is similar to hepatitis C. There is limited knowledge of hepatitis G, which is also transmitted through blood transfusion. In managing hepatitis infection, histone deacetylase inhibitors played an essential role.

3.2.1. Histone deacetylase inhibitors suppressed hepatitis-C progression.

Progression of the hepatitis C virus depends upon the acetylation and methylation of histone protein. As per previous studies, we came to know that suberoylanilide hydroxamic acid effectively inhibited the replication of the hepatitis C virus. Liver infection and inflammation positively regulated the occurrence of hepatitis but liver-expressed antimicrobial protein-1 negatively regulated the infection. The Hepatitis C virus increases the amount of iron in the liver.Binding of protein alpha, hypoxia-induced factor, and transcription factor accumulated iron in the liver. So, we understood that increased expression of antimicrobial protein-1 negatively regulated the progression of hepatitis C virus infection. In this way to establish the statement, Zhou *et al.* experimentally proved that some histone deacetylase-3 inhibitors like suberoylanilide hydroxamic acid, trichostatin-A, and RGFP966 (**13**) were used to inhibit hepatitis C virus and the progression of hepatocellular cancer. Outcomes revealed that trichostatin showed maximum inhibition of hepatitis c virus progression. It was also observed that suberoylanilide hydroxamic acid minimized hepatitis c virus messenger ribonucleic acid levels, and RGFP966 and suberoylanilide hydroxamic acid positively increased the level of liver-expressed antimicrobial protein-1. These data confirmed the statement that histone deacetylase inhibitors-3 inhibitors effectively suppressed the progression of the hepatitis C virus [36].

3.2.2. Impact of Histone deacetylase 6 on hepatitis C virus.

Previous studies suggested that histone deacetylase 6 inhibitors suppressed the growth of tubulin microtubules, and hyperacetylation of the tubulin microtubule also impacted histone

deacetylase gene expression. Also, expression of class-III histone deacetylase SIRT-2 positively impacted tubulin deacetylation, leading to neuronal disorders. Host actin-tubulin interacted with NS3 and NS5A proteins navigated toward hepatitis C virus replication. It was also noticed that microtubule accumulation inhibitors vinblastine and colchicine did not positively impact hepatitis C virus replication. So, Kozlov *et al.* experimentally proved the role of histone deacetylase 6inhibitorstubostatin-A (**14**) and2-[3-(2-phenylethoxy)anilino]benzamide (**15**) on the progression of hepatitis C virus replication. In this way, green fluorescent activity using luciferase enzyme and cell viability assay using Huh7-Luc/neo cells and Huh7 cells were performed with tubostatin A and C-33a, which showed that tubostatin-A gradually decreased both the activity but C-33a up to 10 micromolar concentration viral growth. Still, after that concentration range, it suppressed the growth, but C-33a gradually inhibited the viable cell count. Then acetylation levels of alpha-tubulin on HepG2, Huh7, and Huh7-Luc/neo cell lines suggested that C-33a was weakly acetylated the tubulin protein whereas strongly acetylated in the presence of tubostatin-A and the correlation studies stated that tubostatin-A negatively regulated the progression of hepatitis C virus replication on Huh7, and Huh7-Luc/neo cell line. These data collectively confirmed the importance of tubostatin-A in the growth inhibition of the hepatitis C virus [37].

3.2.3. N-Propylhydrazide derivative of hydroxamic acid derivatives in the treatment of hepatitis C virus.

As per the pharmacophoric features of established hydroxamic acid derivatives, it was observed that the zinc-binding group creates a positive impact on receptor-ligand interaction. In the structure of hydroxamic acid derivatives, in the terminal position –the NHOH group was present, but in this article, Kozlov *et al.* changed the terminal group with propyl hydrazide (-NH-NH-CH2-CH2-CH3) group to identify the impact on receptor identification and inhibitory effect on hepatitis C virus infection. In this experiment, phenylhydrazide derivatives of N-hydroxy-4-[(2-methyl-1H-benzimidazol-1-yl)methyl]benzamide, cinnamic acid, phenylbenzohydroxamic acid, 3-phenylpropanhydroxamic acid, and N-hydroxy-9H-xanthene-9-carboxamide, tubostatin- A, belinostat, and vorinostat were synthesized upon reaction with substituted propylhydrazide followed by inhibition of hepatitis C virus replication. Outcomes revealed that most hydrazide derivatives worked via histone deacetylase 1, 2, and 3 subtypes except N-hydroxy-9H-xanthene-9-carboxamide. Also, antiviral activities suggested that 4-[(2-methyl-1H-benzimidazol-1-yl)methyl]-N'-propylbenzohydrazide (16) showed good anti-hepatitis C activity than the parent molecule with 0.025 micromolar effective concentration. These data confirmed that these propylhydrazide derivatives effectively worked on hepatitis C virus infection [38].

In another research, Kozlov *et al.* developed twelve pyridine-linked hydroxamic acid derivatives followed by an evaluation of hepatitis C virus inhibition and established the correlation between synthesized molecules and inhibition of hepatitis C virus replication. Outcomes revealed that N-hydroxypyridine-2-carboxamide (17), N-hydroxypyridine-3-carboxamide (18) and N-hydroxypyridine-4-carboxamide (19) showed good anti-hepatitis C virus activity with accumulated alpha-tubulin information as compare to N-hydroxybenzamide [39].

3.3. Role of HDACI on other viruses.

3.3.1. Histone deacetylase inhibitors in the treatment of the respiratory syncytial virus.

The respiratory syncytial virus is responsible for the infection of the lungs and air passages. In the US, a maximum number of children are infected with this virus, and worldwide almost 60 million are infected with this virus. Among them, 1.6 lakh people die every year. In treating this virus, Feng et al. experimentally proved the histone deacetylase inhibitors in treating the respiratory syncytial virus. This experiment treated bronchial epithelial cell line BEAS-2B with 500 nanomolar concentrations of trichostatin-A and suberoylanilide hydroxamic acid. Replication of the respiratory syncytial virus and levels of RIG-I receptor messenger ribonucleic acid and interferon-beta1 were evaluated. Outcomes said that trichostatin-A showed maximum inhibition of respiratory syncytial virus and increased levels of both messengers. It was also observed that the levels of inflammatory factors like interleukin-6, interleukin-8, nitrous oxide, and malonaldehyde were reduced by trichostatin-A. These data confirmed the importance of histone deacetylase inhibitors in suppressing this virus [40].

3.3.2. Reactivation of latent herpes simplex virus using histone deacetylase inhibitors.

As for HIV, latency is the major problem associated with herpes simplex virus activity. In latent form, all the genetic characteristics were suppressed and not responsive to antiviral therapy. There was a latency-associated transcript promoter gene observed in the herpes simplex virus DNA sequence, and this promoter sequence was further linked with acetylated H3 histone protein. This acetylated histone was responsible for chromatin remodeling. Also, a recent study suggested that herpes viral DNA and cell polypeptide ICP0 were interlinked with each other; this interaction makes the viral protein open for amendment by acetylated histone protein. Danaher *et al.* experimentally confirmed the role of histone deacetylase inhibitors (trichostatin-A and suberoylanilide hydroxamic acid) in the reactivation of the virus. By doing so, QIF-PC12 cell was used to study the cumulative reactivation of herpes simplex virus, dLAT2903 (latent promoter gene deletion mutant of McKrae), and McKrae (Herpes Simplex Virus-1 strain with a very high in vivo spontaneous reactivation rate) in the presence of acycloguanosine, forskolin, and other external mediators. Outcomes showed that higher cumulative reactivation of herpes virus was observed with trichostatin-A compared to forskolin, heat shock treatment. Also, it was observed that up to 8 days of treatment with trichostatin-A, latent mutant strains of the virus were reactivated. These data confirmed histone deacetylase inhibitors' role in managing herpes simplex virus infection [41].

3.3.3. Treatment of oncolytic herpes simplex virus by histone deacetylase inhibitor.

The oncolytic herpes simplex virus is directly related to breast cancer progression. In this manuscript, Cody *et al.* experimentally proved the importance of histone deacetylase inhibitors (belinostat, entinostat, panobinostat (**20**), suberoylanilide hydroxamic acid, trichostatin-A, sodium butyrate, and valproic acid) in the inhibition of MDA-MB-231 (epithelial cells obtained from adenocarcinoma), MCF-10A and 4T1 (human breast cancer cell lines). Outcomes showed that panobinostat, belinostat, and trichostatin-A were observed with 0.03 micromolar, 0.01 micromolar, 0.05 micromolar; 0.3 micromolar, 0.2 micromolar, 0.3 micromolar; and 0.2 micromolar, 0.3 micromolar, 0.05 micromolar associated with MDA-MB-

231, MCF-10A and 4T1 cell lines, respectively. As well as panobinostat, belinostat, entinostat, and vorinostat effectively increased the replication of the virus. These data confirmed the role of these histone deacetylase inhibitors in the management of the oncolytic herpes simplex virus associated with breast cancer [42].

3.3.4. Sodium butyrate increased Human T-lymphotropic virus activity.

The human T-lymphotropic virus is responsible for blood cancer and the generation of inflammatory responses. This virus is encoded with Tax protein which creates a positive impact on the viral cycle. Expression of this protein is linked with $CD4^+$-T cells and $CD8^+$-T cells. Removal of $CD8^+$-T cells increased the expression of the viral gene in peripheral blood mononuclear cells. Acetylation of histone protein and methylation of deoxyribonucleic acid linked with viral expression. Acetylated histone is maintained by the functionalities of histone acetyltransferase and histone deacetylase enzymes. Histone acetyltransferase is also responsible for the unfolding of chromatin, and the histone deacetylase enzyme minimizes the rate of transcription. In this manuscript, Mosley *et al.,* expressed the importance of histone deacetylase inhibitors in managing the T-lymphotropic virus and the expression of $CD8^+$-T cells. Outcomes showed that trichostatin-A was observed with maximum Tax protein expression in the infected cells, and sodium butyrate was observed with similar activity. It was also observed that sodium butyrate improved Tax protein expression [43].

3.3.5. Small non-coding micro RNA in the treatment of influenza.

The influenza virus belongs to *Orthomyoxoviridae* family, and it has mainly two types Influenza A and B. H1N1 and H3N2 are the subtypes of influenza A virus, and influenza B (Victoria) and influenza B (Yamagata) are the two lineages of influenza B virus [44]. Hemagglutinin, neuraminidase, and M2 proton channel are the spike proteins of the influenza virus. A viral protein, M1, is present just below the lipid layer, and within the virus core protein, viral ribonucleic acid is present. Another protein (nuclear export protein) is inside the core viral genome. Most of the strains of the influenza virus undergo mutations using viral antigens. Mainly antigenic drift and shift are used as tools for viral mutation involving hemagglutinin and neuraminidase proteins. This continuous mutation makes the anti-influenza drugs fail to prove their point. These constant mutations are halted by micro RNA (small non-coding RNA). Xia *et al.* experimentally proved the importance of miRNA in treating the continuously evolving influenza virus. In this manuscript, A549 (human alveolar adenocarcinoma cell) was infected with H5N1 and H1N1, followed by treatment with miR-21-3p microRNA [45, 46]. After applying the micro RNA, interferon beta, small cytokine, and tumor necrosis factor-alpha were evaluated; these factors correlate with influenza virus progression. Results showed that miR-21-3p effectively minimized all the inflammatory mediators and influenza virus levels by targeting histone deacetylase 8 (Figure 5) [47].

Another research observed that inside the influenza virus ribonucleoprotein, some viral enzymes such as nucleoprotein and single-stranded viral ribonucleic acid are observed [48]. Nucleoprotein is an important factor in the replication and progression of the influenza virus. TANK-binding kinase 1- Interferon regulatory factor 3 (TBK1- IRF3) is another factor for controlling influenza virus replication [49]. Acetylation of the TANK-binding kinase 1 enzyme triggered the attachment of interferon regulatory factor-3. Deacetylation of the kinase enzyme

at lysine amino acid residues (241 and 692) triggered the initiation of the TBK1 enzyme;this pathway was activated by the histone deacetylase-3 enzyme [50].

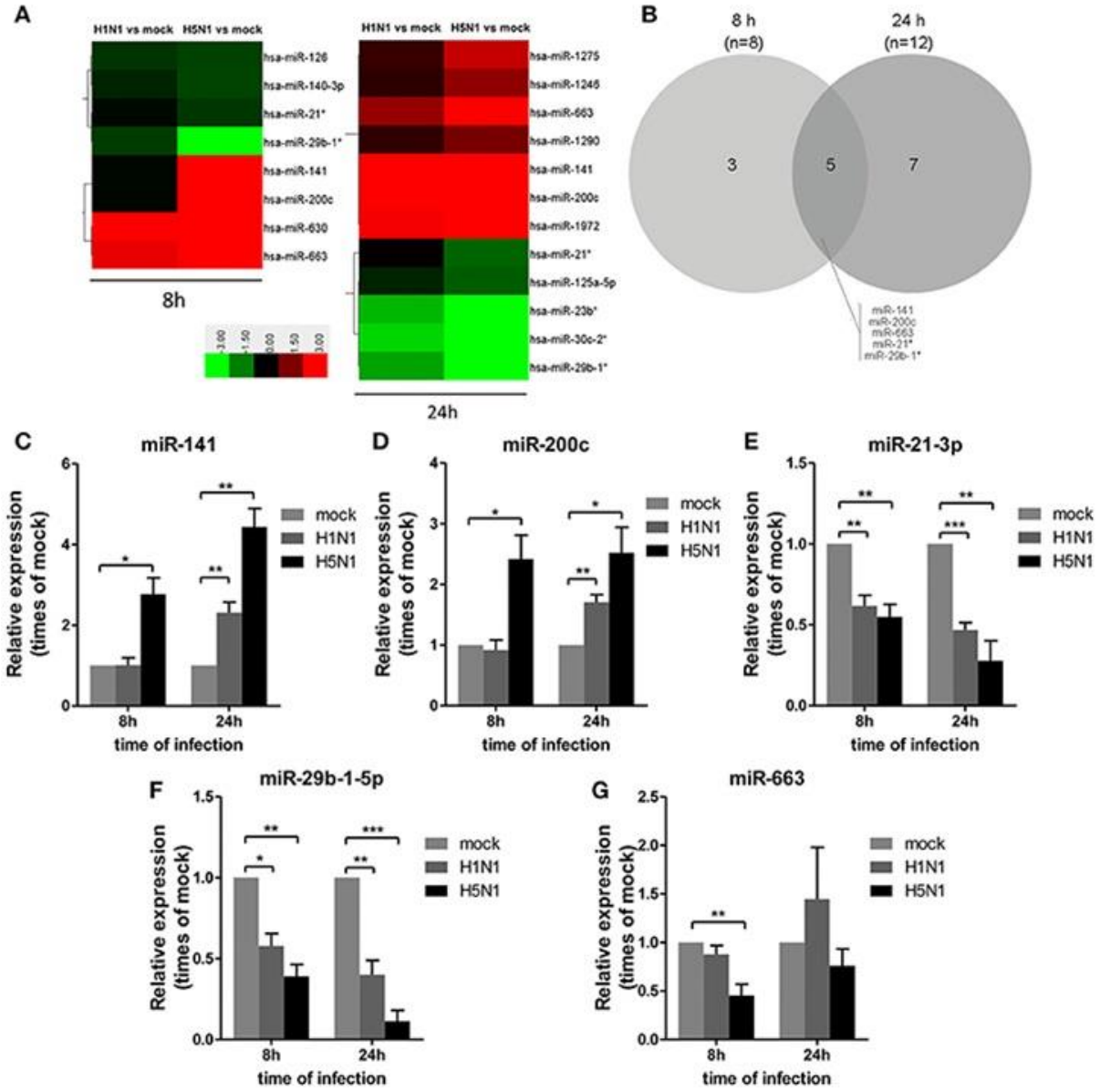

Figure 5. Micro RNA expression during influenza A virus infection as expressed on A549 cells [47].

Chen *et al.* established the role of histone deacetylase-1 enzyme in managing the influenza virus through the acetylation of nucleoprotein. This work linked the histone deacetylase enzyme with hemagglutinin infected with Myc antibody-linked nucleoprotein. After three days of incubation and analysis of linked antibodies, nucleoprotein directly intermingled with histone deacetylase-1 enzyme. The researcher introduced trichostatin-A to confirm the role of histone deacetylase-1 in the acetylation of the nucleoprotein. Results showed that K103, 227, 229, and 470 acetyl-lysine residues were observed in the nucleoprotein without applying trichostatin-A, and the levels of K91, and K198 lysine residues were higher after the application of trichostatin-A (Figure 6). Finally, it was observed that the initiation of the TBK1- IRF3 pathway minimized the presence of the histone deacetylase-1 enzyme. These data confirmed the role of the histone deacetylase-1 enzyme in controlling the progression of the influenza virus [51].

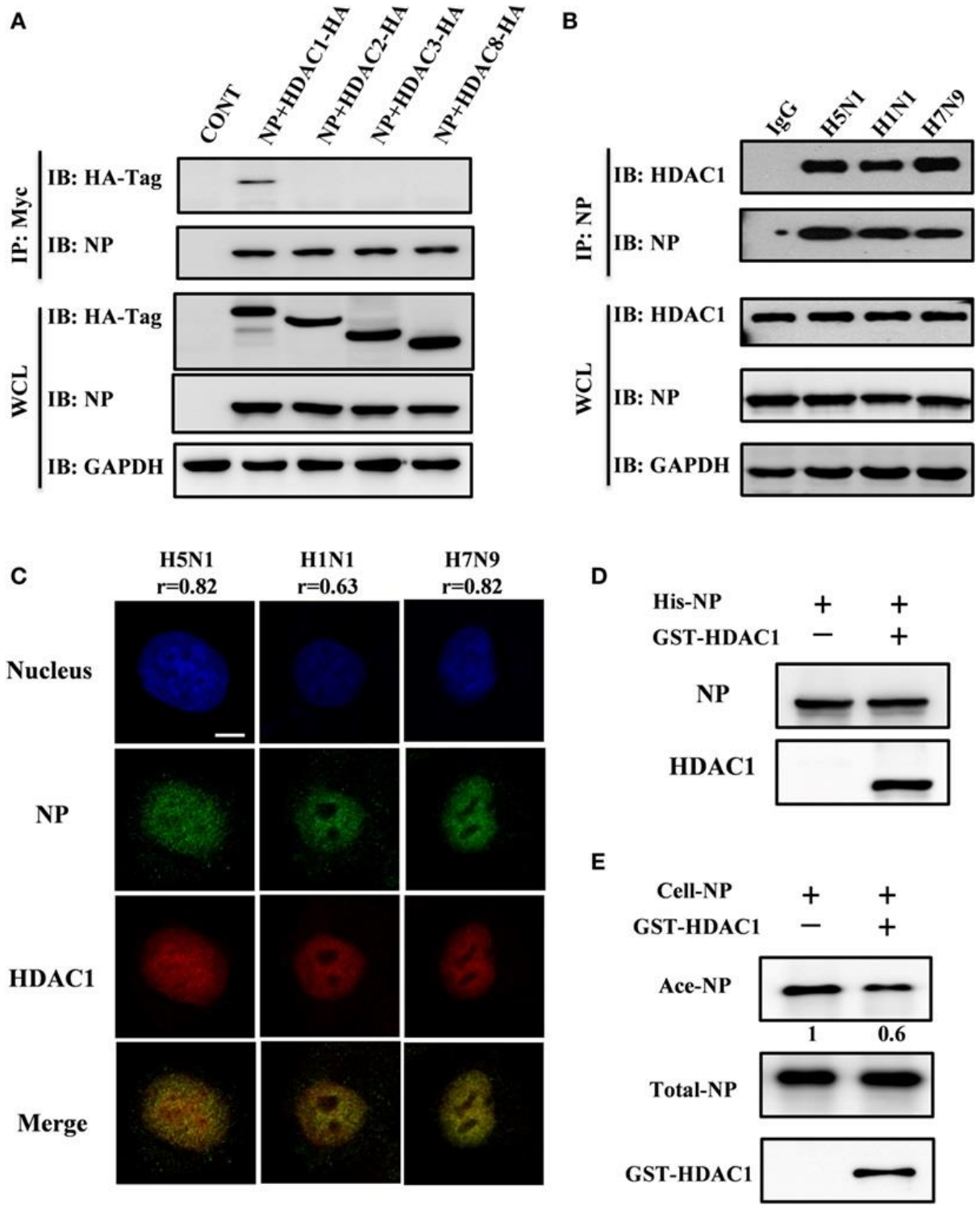

Figure 6. Nucleoprotein interacted with HDAC1 enzyme, co-expressed with HDAC1, HDAC2, HDAC3, or HDAC8 in HEK293T cells [51].

6. Discussion

In this manuscript, we focused on the role of histone deacetylase inhibitors in managing viral infections. Class I and II histone deacetylase enzymes were mainly involved in these treatments. We observed that the HDAC enzyme is mainly associated with HIV, hepatitis, herpes, and influenza. Most research mainly focused on developing newer HDAC inhibitors to reactivate latent HIV virion. Ethyl ketone derivatives(azaspiro carboxamide and imidazolyl nonanone), panobinostat, vorinostat, largazole, entinostat, bryostatin, trichostatin-A, NCH-51, NCH-47 as HDAC inhibitors effective against HIV infection through direct inhibition of the

viral protein or reactivate the latent HIV virion by targeting HDAC 1,2, 3, 6 and 8 receptors. SAHA, RGFP966, anilinobenzamide derivative, propyl benzhydrazide derivative, N-hydroxy-pyridine-2/3/4-carboxamide showed marked inhibition of hepatitis B and C virus. Trichostatin-A, panobinostat, belinostat, entinostat, and vorinostat were effective against respiratory syncytial and herpes viral infections. In the case of influenza virus treatment, small non-coding micro RNA miR-21-3p and trichostatin-A showed marked inhibition of continuously mutated influenza virus.In the development of the antiviral agents, structural features of the molecules said that spiro compounds attached with quinolone-imidazolyl carboxamide, indolyl/ thiazolyl/ anilinobenzamide/ naphthalene hydroxamic acid, dimethylaminophenyl/ phenylthiazolyl/ pyridoindolyl group with or without straight-chain alkane (up to 7 carbons), benzothiazole, phenylethoxanilinobenzhydrazide groups were mainly introduced in the structures as well as substituted/structural similar hydroxamic acid derivatives were also available.

7. Conclusions

As we know, HDAC enzyme is mainly associated with the occurrence and progression of cancer. But here, HDAC enzyme has an important role in the progression of different viral infections. As per the study, we came to know that HDAC 1, 2, 3, 6, and 8 enzymes are associated with viral replications. Scientists explored the relationship between HDAC enzyme and the progression of HIV, hepatitis-B/C, herpes simplex, influenza, and other respiratory viruses. Among all the established and synthesized HDAC inhibitors, SAHA, trichostatin-A, vorinostat, panobinostat, entinostat, and RGFP966 showed good activity. As per structural features, quinolone, indole, thiazole, benzimidazole, and pyrazole heterocyclic groups show remarkable results. So, if the sufficient focus is imposed on developing newer generation HDAC inhibitors to conquer viral manifestation and replication, it will work as a boon to mankind. Also, among huge natural abundance, only one diterpene from *Cousiniaalata*Schrenk was targeted on the HDAC enzyme. So, there are huge natural sources still unexplored. There are more than 25 plant species available to conquer various viral replications. So, the bottom line is if, in the future, the development will target the exploration of natural resources and the development of semi-synthetic or structurally similar HDAC inhibitors, it would be charismatic to humanity to mitigate various viral infections collectively.

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Conflict of Interest

The authors have no conflicts of interest, financial or otherwise.

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