

INHIBITION OF HISTONE DEACETYLASE LIKE PROTEIN: INSIGHTS FROM COMPUTATIONAL STUDIES

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Histone deacetylase (HDAC) enzymes modify the histone protein by removing the acetyl group from the lysine residues, known as histone deacetylation. HDACs have been reported to be involved in the alteration of gene expressions of cancer suppressor proteins, resulting in the development of the cancer cells in the human body. Many recent studies have proven that inhibition of HDAC significantly contributes to the control of cancer growth. Therefore, HDAC inhibitors have been considered promising anticancer agents. Several HDAC inhibitor compounds are currently in different stages of clinical trials. This study is focused on studying the impact of HDAC inhibitors on the stability of the histone deacetylase like protein (HDLP) through computational techniques. The selected inhibitors for this study are SAHA (suberoylanilide hydroxamic acid/vorinostat), LBH589 (panobinostat), and PXD101 (belinostat). SAHA is considered as a reference drug because it is a well-known drug in clinical practices. Molecular dynamics (MD) studies were used to investigate the atomic level description of drug binding sites and how the HDAC inhibitors change the environment of the active site of the HDLP. The inhibition potent was analyzed in terms of hydrogen bond analysis, secondary structure analysis, and interaction energy analysis. This work was carried-out with molecular docking and MD simulations for 100 ns with the gromos53a6 force field, and the resultant trajectories of the HDLP-inhibitor complexes were analyzed. The results contributed to examine and compare the stability of the mutated HDLP in HDLP-inhibitor complexes in the aqueous environment. The results revealed that the HDLP-LBH589 complex has greater interaction energy ($-303.98 \pm 5.9 \text{ kJ mol}^{-1}$), a higher number of amino acids in alpha-helix (129) secondary structures and an increased number of hydrogen bonds (5) compared to other two systems. Therefore, the LBH589 complex has greater stability. According to this study, the stability order varies as HDLP with LBH589 > SAHA > PXD101. This theoretical observation is correlated with experimental IC₅₀ values of LBH589 (5 nM), SAHA (10 nM), and PXD101 (27 nM). Therefore, the findings revealed that LBH589 is more potent than SAHA to stabilize HDLP. Therefore, the use of LBH589 in the clinical application will give more effective results to cure epigenetically caused cancer.

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