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Insights from Computational Approach to Predict the Inhibitory Efficacy of the HDAC Inhibitor on HDLP Enzyme

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The nucleosomes transfer the epigenetic information to the lysine residue associated with the histone protein, results from epigenetic modification in lysine. The modifications are governed by the histone deacetylase (HDAC) enzyme. HDACs induce alterations in the gene accessibility in the human body leads to grow cancer. Recent studies showed that HDAC inhibitors are more potent anticancer agents. Suberoylanilide hydroxamic acid (SAHA) is an approved drug by FDA and SAHA is a reference drug in this study. This preliminary work done by the computational technique can assess the inhibitory efficacy of the HDAC inhibitors on histone deacetylase-like protein (HDLP), which reduces the investment and time in cancer research. Also, this study investigates the atomic-level description of the inhibitor binding site of the HDLP and the changes that occurred in the active site due to the inhibitor binding. The inhibitors used for this study are SAHA, trichostatin-A (TSA), and scriptaid (GCK1026). The crystal structure of HDLP was downloaded from the PDB server and the structure of the inhibitor was optimized by Gaussian 9. AutoDock Vina has selected the best binding score of the complex and the best one used to initiate molecular dynamics simulation. The best binding scores of SAHA, TSA, and GCK1026 are -7.9, -8.7, and -6.4 kcal/mol. The trajectories were used to perform the structural analysis. The results of Ramachandran plot and dssp shown that the HDLP with SAHA and TSA contains more percentage of amino acids is favored regions (88.2%, 76.6%) and more amino acids belong to alpha-helical structure (36.42%, 38.05%), which drive the HDLP to a stabilized state. The results revealed that the TSA and SAHA have more potential to stabilize the HDLP than GCK1026. The stabilization efficacy is correlated with the linker length and the IC50 of the SAHA (6.27Å, 10nM), TSA (7.82Å, 1.8nM), and GCK1026 (4.93Å, 39nM). Therefore, it's evident that TSA can use as an alternative to SAHA to inhibit the HDLP.

Keywords*: HDAC enzyme, MD simulation, Ramachandran plot*