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Exploring Valproic Acid (VPA) Analogues Interactions with HDAC8 Involved in VPA Mediated Teratogenicity: A Toxicoinformatics Analysis

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Abstract : Valproic acid (VPA) is the first synthetic therapeutic agent used to treat epileptic disorders, which account for affecting nearly 1% world population. Teratogenicity caused by VPA has prompted the search for next generation drug with better efficacy and lower side effects. Recent studies have posed HDAC8 as direct target of VPA that causes the teratogenic effect in foetus. We have employed molecular dynamics (MD) and docking simulations to understand the binding mode of VPA and their analogues onto HDAC8. A total of twenty 3D-structures of human HDAC8 isoforms were selected using BLAST-P search against PDB. Multiple sequence alignment was carried out using ClustalW and PDB-3F07 having least missing and mutated regions was selected for study. The missing residues of loop region were constructed using MODELLER and energy was minimized. A set of 216 structural analogues (>90% identity) of VPA were obtained from Pubchem and ZINC database and their energy was optimized with Chemsketch software using 3-D CHARMM-type force field. Four major neurotransmitters (GABAt, SSADH, α-KGDH, GAD) involved in anticonvulsant activity were docked with VPA and its analogues. Out of 216 analogues, 75 were selected on the basis of lower binding energy and inhibition constant as compared to VPA, thus predicted to have anti-convulsant activity. Selected hHDAC8 structure was then subjected to MD Simulation using licenced version YASARA with AMBER99SB force field. The structure was solvated in rectangular box of TIP3P. The simulation was carried out with periodic boundary conditions and electrostatic interactions and treated with Particle mesh Ewald algorithm. pH of system was set to 7.4, temperature 323K and pressure 1atm respectively. Simulation snapshots were stored every 25ps. The MD simulation was carried out for 20ns and pdb file of HDAC8 structure was saved every 2ns. The structures were analysed using castP and UCSF Chimera and most stabilized structure (20ns) was used for docking study. Molecular docking of 75 selected VPA-analogues with PDB-3F07 was performed using AUTODOCK4.2.6. Lamarckian Genetic Algorithm was used to generate conformations of docked ligand and structure. The docking study revealed that VPA and its analogues have more affinity towards 'hydrophobic active site channel', due to its hydrophobic properties and allows VPA and their analogues to take part in van der Waal interactions with TYR24, HIS42, VAL41, TYR20, SER138, TRP137 while TRP137 and SER138 showed hydrogen bonding interaction with VPA-analogues. 14 analogues showed better binding affinity than VPA. ADMET SAR server was used to predict the ADMET properties of selected VPA analogues for predicting their druggability. On the basis of ADMET screening, 09 molecules were selected and are being used for in-vivo evaluation using Danio rerio model.

Keywords : HDAC8, docking, molecular dynamics simulation, valproic acid
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