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Study to test the binding of thc- δ9-tetrahydrocannabinol & derivatives on Acetylcholine binding protein (AChbp): A virtual screening & molecular docking study

S.A.H. Naqvi[5], P. P. Panigrahi[1], T. R. Singh[1], R. Singla[2], C. Jayaram[3] and R. Sriram[4]
[1]Jaypee University for Information Technology, India
[2]Central University of Punjab, India
[3]Bangalore University, India
[4]Jeppiar College or Engineering, India
[5]Bio Discovery- Solutions for future , India

Acetylcholinesterase, also known as AChE, is an enzyme found in the synapse between nerve cells and muscle cells. It waits patiently and springs into action, soon after a signal is passed, breaking down the acetylcholine into its two component parts, acetic acid and choline. Acetylcholinesterase is the target of many Alzheimer's Dementia drugs which block the function of acetylcholinesterase and thus cause excessive acetylcholine to accumulate in the synaptic cleft. ACh hydrolysis by AChE causes termination of cholinergic neurotransmission therefore, compounds which inhibit AChE might significantly increase the levels of ACh depleted in AD. Indeed, it was shown that AChE inhibitors improve the cognitive abilities of AD patients at early stages of the disease development.

In order to reveal the binding mode of the derivatives of delta-9-tetrahydrocannabinol (Δ^9-THC) with AChBP, the study is conducted. Mature AChBP is 210 residues long and forms a stable homopentamer.

Molecular docking approach using Lamarckian Genetic Algorithm was carried out to elucidate the extent of specificity of AChBP towards different classes of Δ9-THC. Combining a novel algorithm for rapid binding site identification and evaluation with easy-to-use property visualization tools, the software has provided an efficient means to find and better exploit the characteristics of ligand binding sites. Total number of molecules were 3000 in number which were virtually screened from different databases on the basis of the structural similarity of Δ9-THC.

The docking result of the study of 3000 molecules demonstrated that the binding energies were in the range of -14.34 kcal/mol to -3.26 kcal/mol, with the minimum binding energy of -14.34 kcal/mol. 8 molecules showing hydrogen bonds with the active site residue TRP 143.

The molecule S1, binding energy -12.03 kcal/mol showed Drug Likeness score of 0.14 with Mol PSA as 30.88 A^2 and MolVol as 474.48 A^3. The MolLogS was -0.99 with solubility of -6.04 and drug score of 0.12. The molecule showed no indication for mutagenicity, & tumorigenicity. Also, no indication for irritating & reproductive effects found. Further in-vitro and in-vivo study is required on these molecules as the binding mode provided hints for the future design of new derivatives with higher potency and specificity.