EVALUATION OF THE BINDING MODE OF CANNABINOID DERIVATIVES AT THE 5-HT1A RECEPTOR THROUGH *in silico* APPROACHES

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Introduction

Cannabis sativa, used for over a millennium, was first documented in China [1] around 4000 B.C, initially cultivated for its fibers and later recognized for its medicinal properties [2]. Despite ancient reports of its therapeutic use, research into its clinical potential has only recently intensified. Based on the central effects of *C. sativa*, such as relief from anxiety, pain, and thermoregulation, one potential molecular target for the action of cannabinoid derivatives is the serotonin receptor 5-HT1A [3]. Therefore, the present study aimed to evaluate the binding modes of the ten main phytocannabinoids reported in the literatue with the 5-HT1A receptor through molecular docking. Additionally, the permeation and retention of these compounds in the blood-brain barrier (BBB) were investigated, as well as their potential as substrates for P-glycoprotein (P-gp).

Material and Methods

Molecular docking was performed using the GOLD program. The 5-HT1A three -dimensional structure was obtained from the Protein Data Bank (PDB 7E2Z), and the ligands were retrieved from DrugBank. Protein preparation was carried out via the PlayMolecule server, while the ligands were prepared using the Avogadro program. Docking simulations were conducted after a redocking step with the CHEMPLP scoring function. The binding modes of cannabinoid derivatives at the 5-HT1A receptor were analyzed using PyMol and LigPLOT programs. Blood-brain barrier (BBB) permeability potential and P-glycoprotein (P-gp) substrate assessments were conducted using ADMET Predictor™ v.11 and the SwissADME server.

Results and Discussion

The most favorable binding site was validated using cannabidiol (CBD) as a reference for docking into the receptor, followed by analyses of the other phytocannabinoids, selecting the poses with the highest affinity. The CBD derivative showed the same hydrogen bonds with the residues ASP116 and TYR390 as the co-crystallized ligant, aripiprazole. BBB permeation analyses indicated that all derivatives could cross the BBB. P-gp substrate predictions revealed that 9 derivatives, according to ADMET Predictor™ v11, and 7 derivatives, according to SwissADME, were not substrates of P-gp. LogBB analyses further confirmed that all derivatives were retained in the BBB. Furthermore, the derivatives that showed better scoring functions are expected to have higher affinity with the receptor, as was the case for CBC, DCBF, CBG, CBF, along with CBD.

Conclusion

Based on the computational analyses performed, the ability of the key cannabinoids to cross the BBB for a central effect was demonstrated. Additionally, the interaction mode of the main components of Cannabis oil with the 5-HT1A receptor was elucidated, highlighting their therapeutic potential.

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