Improvement in binding affinity of Ginkgolide B in comparison to Levodopa: A molecular docking Study

Rumpa Banerjee¹, Riya Adhya¹ and Abhimanyu Thakur²*

¹Department of Pharmaceutical Chemistry, Bharat Technology, Uluberia, Howrah, India
²Department of Biomedical Sciences, City University of Hong Kong, 83, Tat Chee Avenue, Hong Kong SAR

ABSTRACT

Parkinson’s disease involves the malfunction and death of vital nerve cells in the brain called neuron which produce dopamine, a chemical that sends message to the part of the brain that controls movement and coordination. As Parkinson’s disease progresses, the amount of dopamine produced in the brain decreases, leaving a person unable to control movement normally. The test drug Ginkgolide B and standard drug Levodopa have targeted the protein D² receptor (PDB ID: 2YOU) and protein D³ receptor (PDB ID: 3PBL) respectively. Both the test and standard drug were drawn using Chemsketch draw software and structures were optimized using Arguslab software. Then they were docked with the Dopamine D² protein (PDB ID: 2YOU) and Dopamine D³ protein (PDB ID: 3PBL) using HEX software. The test drug showed improvement in binding affinity and other properties in comparison to standard drug.

Keywords: Parkinson’s disease, 2YOU, 3PBL, Hex docking, Chemskech.

INTRODUCTION

Parkinson’s disease is a progressive disease of the nervous system marked by tremor, muscular rigidity, and slow, unfocused movement, chiefly affecting middle-aged and elderly people. It is associated with degeneration of the basal ganglia of the brain and a deficiency of the neurotransmitter dopamine [1]. Levodopa is the most effective medicine to control the symptoms of Parkinson’s disease. Dopamine receptors are a class of G-protein coupled receptors that are prominent in the central nervous system. The two types of dopamine receptors are D¹ like and D² like. D¹ like receptors includes D¹ and D₅ receptors which are associated with stimulation of adenylate cyclase and D² like receptors includes D₂, D₃, D₄ receptors subtypes which are associated with inhibition of adenylyl cyclise [2].

Ginkgo biloba is found in China, useful for dementia, Alzheimer’s and Parkinson’s disease [1-3]. Active ingredients in ginkgo leaves include flavonol glycosides and terpene trilactones, principally the diterpene ginkgolides A, B, C and J, and the sesquiterpene bilobalide, along with smaller amounts of biflavones, proanthocyanidins, and organic acids [4-6].

Docking is a method by which we can predict the preferred orientation, affinity and activity of a molecule to a targeted protein. The molecular docking tool, Hex 5.1 interface was used for docking and scoring [7-9]. The Protein Data Bank (PDB) file of the structure of ligand was done by using chemsketch draw software and the structure was optimized by using ArgusLab software. The optimized structure was used for molecular docking. The crystal structure of the protein that is the receptor was downloaded from PDB [9-14].
EXPERIMENTAL SECTION

This study was performed using bioinformatics tools, biological databases like Protein Data Bank, Pubmed and software’s like Hex, ACD Chmseketch and Arguslab. From the various literature review it was found that Ginkgolide B, a biologically active constitute of *Ginkgo biloba*, is a diterpenoid trilactone with six five-membered rings. The elucidation of its structure set in 1967 by Maruyama et al. It can be used for the treatment of Parkinsonism, dementia, Alzheimer’s disease. Here in this study we have selected to work with the Parkinson’s disease. So, we have taken Levodopa as the standard drug for docking comparison since Levodopa is the most effective medicine for relieving symptoms of Parkinson’s disease.

ACD Chemsketch which is a dominant universal chemical drawing and graphics package from ACD/Labs developed to help chemists rapidly and easily draw molecules, reactions and schematic diagrams, calculate chemical properties, and design professional reports and presentations. It was used to draw the structure of the standard drug Levodopa and the test drug Ginkgolide B and then its properties were analysed and shown in Table No. 1.

<table>
<thead>
<tr>
<th>Property</th>
<th>Ginkgolide B</th>
<th>Levodopa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>424.398</td>
<td>197.188</td>
</tr>
<tr>
<td>Log P</td>
<td>0.49</td>
<td>-2.39</td>
</tr>
<tr>
<td>H-Bond acceptor</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>H-Bond Donor</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Polar surface area</td>
<td>148.82 Å²</td>
<td>103.78 Å²</td>
</tr>
<tr>
<td>Refractivity</td>
<td>91.38 cm⁻¹</td>
<td>49.08 cm⁻¹</td>
</tr>
<tr>
<td>Rotatable atoms</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Fig.1: 3D Dimensional structure of 3PHL
Fig.2: Dimensional structure of 2YOU

Fig.3: 3D Dimensional structure of 2YOU with Ligand Standard and Ligand Test respectively
The PDB (Protein Data Bank) is used to download the target protein Dopamine D₂ receptor is the PDB ID of the 2YOU protein and the Dopamine D₃ receptor is the PDB ID of the 3PBL protein. It was then used for docking with the protein acting as stimulators. The structures drawn with the help of chemsketch draw software were then optimized using the software Arguslab. The parameter used for optimizing was the Universal Force field.

The docking analysis of Ginkgolide B with 2YOU and 3PBL protein was carried out using HEX 5.1 docking software. This software is an Interactive Molecular Graphics Program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules.

Docking allows predicting the ligand with best scores and identifying the drug receptor complex with lowest free energy. The parameters used for the docking process were:

1. Correlating type - Shape + electrostatic only
2. FFT Mode - 3D fast lite
3. Post processing - None
4. Grid Dimension - 0.6
5. Receptor range - 180
6. Ligand range - 180
7. Twist range - 360
8. Distance range - 40

The test drug Ginkgolide B and standard drug Levodopa were docked with the Dopamine receptor using the above parameters. After docking, the test ligand Ginkgolide B and standard ligand Levodopa with two protein 2YOU and 3PBL gave the affinity results were evaluated.

RESULTS AND DISCUSSION

The docking results of the test drug Ginkgolide B and Levodopa with the protein D₂ receptor (PDB ID: 2YOU) and protein D₃ receptor (PDB ID: 3PBL) are shown in the Table No. 2 and Table No. 3.

<table>
<thead>
<tr>
<th>Compound</th>
<th>E-value</th>
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<tbody>
<tr>
<td>Standard Levodopa</td>
<td>-175</td>
</tr>
<tr>
<td>Test Ginkgolide B</td>
<td>-264</td>
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<table>
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<tr>
<th>Compound</th>
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<tbody>
<tr>
<td>Standard Levodopa</td>
<td>-188</td>
</tr>
<tr>
<td>Test Ginkgolide B</td>
<td>-281</td>
</tr>
</tbody>
</table>
The HEX docking results reveal that the E-value of test drug Ginkgolide B was better as compared to that of the Standard drug Levodopa. The test drug Ginkgolide B showed an increase in the free energy of the complex with the receptor but bonded the receptor in the same binding pocket. This indicated that the functional group involved in the complex formation may be same as that of standard drug.

CONCLUSION

Arguslab and Hex 5.1 software used for docking standard Levodopa and the sample Ginkgolide B with the Dopamine receptor D_{2} protein (PDB ID: 2YOU) and the Dopamine receptor D_{3} protein (PDB ID: 3PBL) and results of sample obtained were consistent with the standard Levodopa. Ginkgolide B was found to be as potent as Levodopa. This binding affinity can be attributed to the strong ligand interaction.

REFERENCES