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Research Article

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

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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 D_2 receptor (PDB ID: 2YOU) and protein D_3 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 D_2 protein (PDB ID: 2YOU) and Dopamine D_3 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, Chemsketch.

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 D_1 like and D_2 like. D_1 like receptors includes D_1 and D_5 receptors which are associated with stimulation of adenylate cyclase and D_2 like receptors includes D_2, D_3, D_4, receptors subtypes which are associated with inhibition of adyenylate 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].

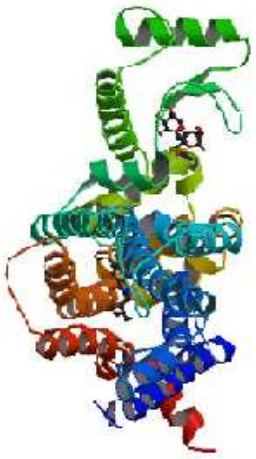

Fig.1: 3 Dimensional structure of 3PBL

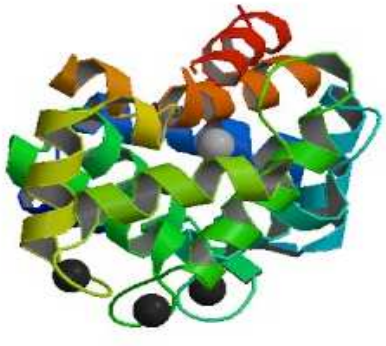

Fig.2: Dimensional structure of 2YOU

EXPERIMENTAL SECTION

This study was performed using bioinformatics tools, biological databases like Protein Data Bank, Pubmed and software's like Hex, ACD Chemsketch 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 No. 1: Properties of Gingolide B and Levodopa

Property	Ginkgolide B	Levodopa
Molecular weight	424.398	197.188
Log P	0.49	-2.39
H-Bond acceptor	7	5
H-Bond Donor	3	4
Polar surface area	148.82 A^2	103.78 A^2
Refracitivity	91.38 cm^3	49.08 cm^3
Rotatable atoms	1	3

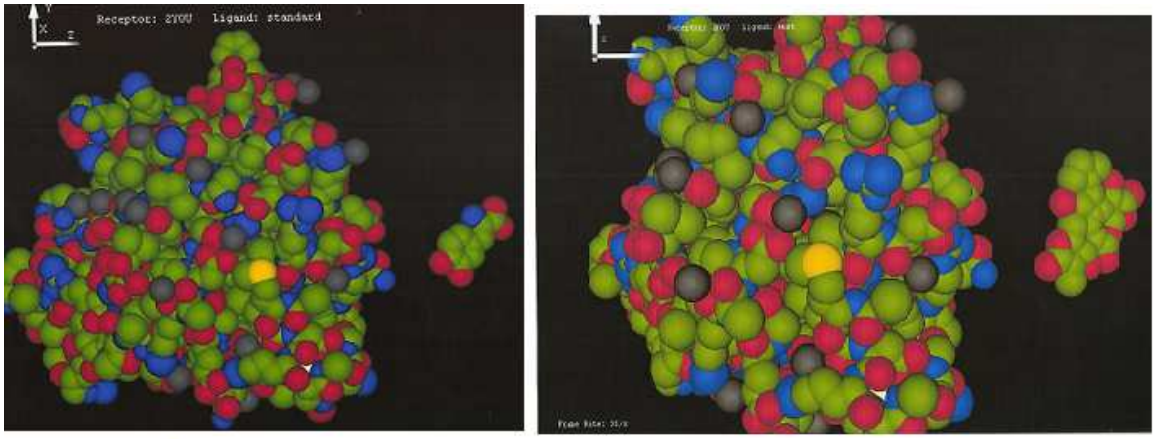

Fig.3: 3 Dimensional structureof 2 YOU with Ligand Standard and Ligand Test respectively

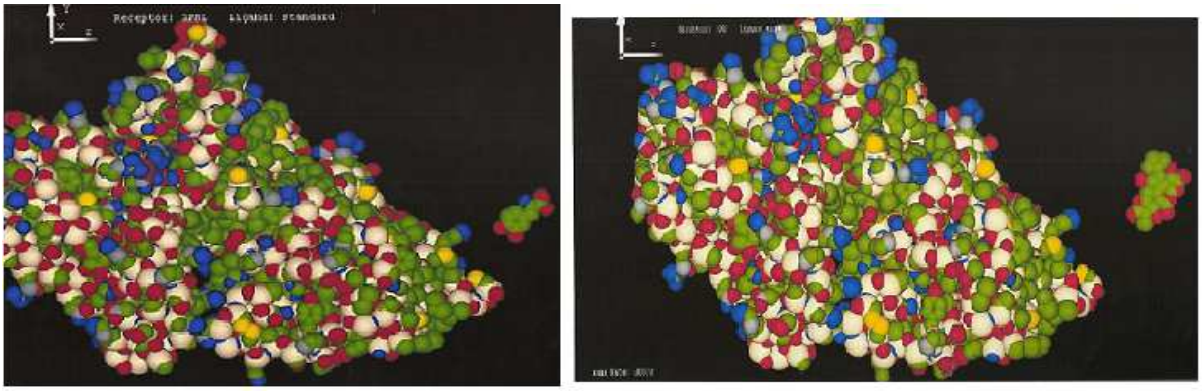

Fig.4: 3 Dimensional structure of 3PBL with Ligand Standard and Ligand Test respectively

The PDB (Protein Data Bank) is used to download the target protein Dopamine D_2 receptor is the PDB ID of the 2YOU protein and the Dopamine D_3 receptor is the PDB ID of the 3PBL protein. It was then used for docked 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 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. Distange 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 D_2 receptor (PDB ID: 2YOU) and protein D_3 receptor (PDB ID: 3PBL) are shown in the Table No. 2.and Table No.3.

Table No. 2: Hex docking results of 2YOU with standard Levodopa and Ginkgolide B

Compound	E-value
Standard Levodopa	-175
Test Ginkgolide B	-264

Table No. 3: Hex docking results of 3PBL with Standard Levodopa and Ginkgolide B

Compound	E-value
Standard Levodopa	-188
Test Ginkgolide B	-281

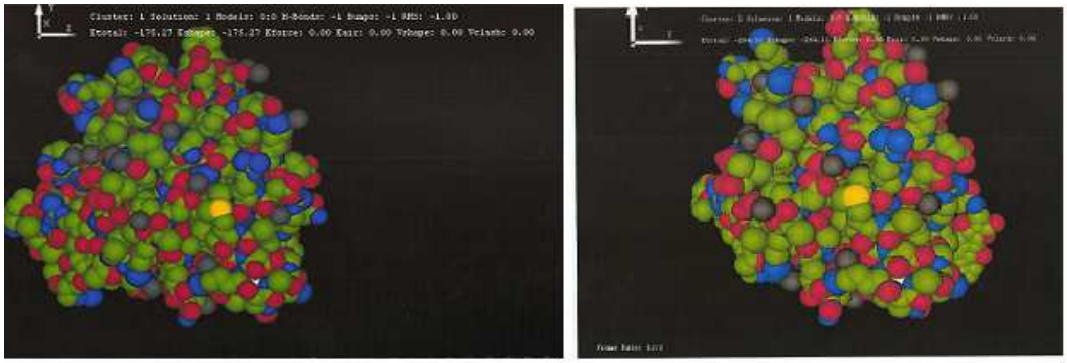

Fig.5: Docking of Ligand Standard and Test with 2YOU respectively

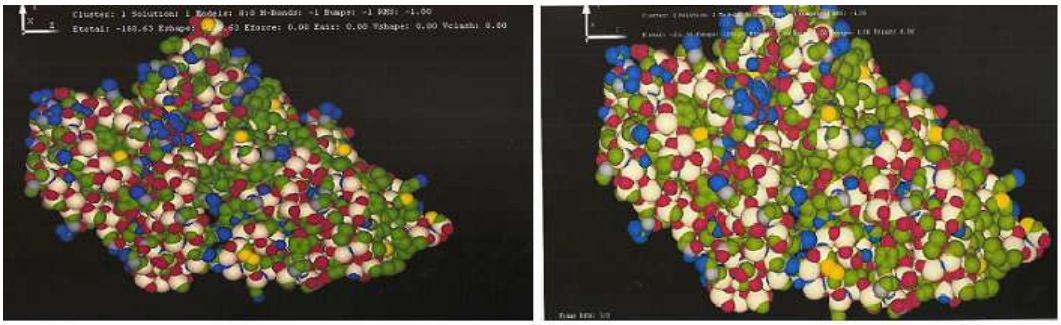

Fig.6: Docking of Ligand Standard and Test with 3PBL respectively.

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.

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