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IMPROVEMENT IN BINDING AFFINITY OF TAMOXIFEN FOR DOPAMINE RECEPTOR: A MOLECULAR DOCKING STUDY

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Abstract
Parkinson’s disease (PD) was first described in 1817 with the publication by James Parkinson of a book entitled ‘An Essay on the Shaking Palsy’. PD occurs due to loss of Dopamine-Synthesizing Neurons in the Brain Stem. The physical appearance of flexed posture, resting tremor, and shuffling gait are readily recognizable. The drugs which are used for dealing PD, affect directly on the Dopamine receptors. We have found that D_2 Dopamine receptor (PDB ID: 5aer) is the significant target of action for drugs used to treat PD. So, we have chosen the receptor 5aer for docking with test ligand (Tamoxifen) and standard ligand (Levodopa). Structures of two test drugs and the standard drug were drawn utilizing Chemsketch software and were optimized in Arguslab software. Subsequently the docking of test and standard drugs with D_2 Dopamine receptor (PDB ID: 5aer) are done in the Hex 6.0 docking software. Thus the improvement in binding affinity of Tamoxifen for Dopamine Receptor was carried out.

Keywords: Parkinson’s disease, Tamoxifen, Hex 6.0, Chemsketch, Arguslab

Introduction
Parkinson’s disease (PD) is caused due to destruction of dopaminergic neurones. Parkinsonian features emerge when more than half of the dopaminergic nerve terminals in the striatum are moved out. Pioneering research half a century ago by neuroscientists Arvid Carlsson and Oleh Hornykiewicz revealed that Parkinsonism could be reversed temporarily by pharmacologic interventions to restore striatal dopaminergic neurotransmission. This reversal can be accomplished by dopaminergic agonists, compounds that directly stimulate postsynaptic striatal dopamine receptors. In this case Levodopa is the most effective medicine to control the PD.\[1\]

Dopamine (DA) is the predominant catecholamine neurotransmitter, where it controls many functions including locomotor activity, emotion, positive reinforcement, food intake, endocrine regulation. The physiological actions of DA are mediated by 5 distinct but closely related G protein-coupled receptors (GPCRs) that are divided into 2 major groups: D1 class & D2 class.\[2\] D1 class contains D1 & D5 dopamine receptors. The D1 and D5 receptors are closely related, and couple to G_s and stimulate adenylyl cyclase activity. D2 class contains D2, D3 & D4 dopamine receptors. D2, D3 and D4 receptors couple to G_i and inhibit the formation of cAMP.\[3\]
Tamoxifen is a non-steroidal agent that has shown potent anti-estrogenic properties and useful in healing of advanced breast cancer in postmenopausal women as well as melanoma, soft tissue sarcoma, Endometrial and Pancreatic Cancer. Moreover it prevents infertility in women with ovulatory disorders. It was discovered in 1967. It mimics the action of estrogen and acts as antineoplastic in breast tissues. From a literature review it was found that Tamoxifen, can be also used to cure of Parkinsonism. So, we have selected it as sample drug.

Computational molecular docking is a computational science aiming at predicting optimal binding orientation and conformation of interacting molecules in space and to estimate stability of their complex. It predicts whether or not the two molecules interact, the binding affinity and the 3D structure of the complex. Here for molecular docking we have used Chemsketch, Argulab and Hex 6.0. The ligands were drawn by means of Chemsketch and were optimized by using Arguslab software. Optimized structure was used for molecular docking with receptor (in Hex 6.0), which was downloaded from Protein Data Bank.

Materials and Methods
In this molecular study Bioinformatic tools, biological databases like PDB, PubMed, different softwares (Hex, ACD/Chemsketch, Arguslab) have been used. From a literature review it was found that Tamoxifen, a biologically active constituent, is used for the treatment of carcinoma with three 6-member rings. Tamoxifen is a synthetic drug. It can be used for the treatment of Parkinsonism, Alzheimer’s disease. Here in this study we have selected to work with the Parkinson’s disease. So, we have taken Levodopa as standard drug for docking comparison, since the Levodopa is the most effective drug for the treatment of PD. Here Chemsketch software has been used to assemble structures of organic molecules, names of organic molecules as well as Lewis structures, 3D structures, space filling models or ball and stick models. Here we have used it to demonstrate the structure and obtain properties of the standard drug Levodopa and the test drug Tamoxifen.

Table 1- Properties of Standard drug Levodopa and Sample drugs Tamoxifen

<table>
<thead>
<tr>
<th>Structure name</th>
<th>Log P</th>
<th>Molecular weight</th>
<th>H-bond acceptor ((\text{nOHNH}))</th>
<th>H-bond donor ((\text{nON}))</th>
<th>Topological Surface Area ((\text{TPSA}))</th>
<th>Molecular Refractive Index ((\text{cm}^3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>-2.20</td>
<td>197.19</td>
<td>5</td>
<td>5</td>
<td>103.78</td>
<td>49.25±0.3</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>6.06</td>
<td>371.52</td>
<td>0</td>
<td>2</td>
<td>12.47</td>
<td>118.89±0.3</td>
</tr>
</tbody>
</table>
The biological database Protein Data Bank is used to obtain the target protein Dopamine 2 receptor (PDB ID: 5aer), which was further used in docking along with test and sample drug. The structures drawn with the help of Chemsketch were then optimized using Arguslab. The parameters used for optimizing was the Universal Force field. The docking analysis of Tamoxifen with 5aer protein was carried out using HEX 6.0. It is an interactive Molecular Graphics Program for calculating docking modes of pairs of protein and DNA molecules. It can also calculate Protein-Ligand Docking, assuming the ligand is rigid, and it can superpose pairs of molecules using only knowledge of their 3D shapes. This software is intended for molecular docking purpose. Molecular Docking predicts the ligand with most excellent scores and identifies the drug-receptor complex with least energy. The parameters used for the docking of test and sample drug with 5aer are given in table 2:

<table>
<thead>
<tr>
<th>Correlating type</th>
<th>Shape only</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFT Mode</td>
<td>3D</td>
</tr>
<tr>
<td>Post processing</td>
<td>None</td>
</tr>
<tr>
<td>Grid Dimension</td>
<td>0.6</td>
</tr>
<tr>
<td>Receptor range</td>
<td>180</td>
</tr>
<tr>
<td>Ligand range</td>
<td>180</td>
</tr>
<tr>
<td>Twist range</td>
<td>360</td>
</tr>
<tr>
<td>Distance range</td>
<td>40</td>
</tr>
</tbody>
</table>

After docking, the test drug Tamoxifen and standard drug Levodopa with receptor 5aer gave the affinity outcomes were evaluated.
Results and Discussion
The docking outcomes of the test drug (Tamoxifen) and standard drug Levodopa with the protein Dopamine 2 receptor (PDB ID: 5aer) are given away in table 3:

**Table 3- Docking Results**

<table>
<thead>
<tr>
<th>Structure name</th>
<th>Hex score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>-184.39</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>-265.28</td>
</tr>
</tbody>
</table>

The outcome molecular docking in Hex 6.0 discloses that the E value of test drug Tamoxifen was better as compared to that of standard drug Levodopa. The test drug showed an increase in free energy of the complex with receptor in same binding pocket. This indicated, that, functional group involved in the complex formation may be same as that of the standard drug Levodopa.

Conclusion
Arguslab and Hex6.0 softwares were used for docking of standard drug Levodopa and sample drugs Tamoxifen with the protein Dopamine 2 receptor (PDB ID: 5aer). Results of sample obtained were consistent with the standard drug Levodopa. Tamoxifen was found to be as potent as Levodopa. The binding affinity can be attributed to the strong ligand interaction.

References


6. BC Cancer Agency CNS Tumour Group; (CNTAMCAR) BCCA Protocol Summary for the Second and Third Line Treatment of Recurrent Gliomas with Carboplatin and High Dose Tamoxifen; Vancouver: BC Cancer Agency; 1 August 2006.


