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Comparative Molecular Docking Studies of Selected Phytoconstituents on Dopamine D3 Receptor (PDB ID: 3PBL) as Potential Anti-Parkinson's Agents †

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Abstract: Parkinson's disease is an idiopathic neurodegenerative disorder which is characterized by the degeneration of the neurons of substantia nigra, a part of the midbrain, regulating the motor movement. It involves a decrease in the levels of dopamine which consequently hampers movement control. In the literature, natural compounds like flavonoids have been cited to exhibit their potential to terminate the augmentation of such a disorder by penetrating the blood-brain barrier. In this study, ten phytoconstituents were screened using molecular docking against Dopamine D3 receptor to identify potential inhibitors. PDB database was employed to extract the target protein of interest, i.e., Dopamine D3 receptor (PDB ID: 3PBL). Both the test drugs and the standard moiety were obtained in their 3D conformation from the PubChem in .SDF format, while FlexX software was used for docking purpose. The docking scores of the selected photochemical were hence compared with levodopa, which was taken as the positive control. The docking studies revealed that Vasicol has the closest docking score (−19.6871 kcal/mol) to that of the standard Levodopa (−23.1188 kcal/mol), proving that it has the best molecular docking result for Dopamine D3 receptor. Also, the low toxicity profile confirmed by pro Tox-II online server indicated that Vasicol is a potential lead to be drug candidate for Anti Parkinson's Disease.

Keywords: Anti-Parkinson's Agents; Dopamine D3 receptor; Vasicol; pro Tox-II; PDB ID: 3PBL

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1. Introduction

Being the second most frequent kind of neurodegeneration, Parkinson's disease is a disorder which is manifested both in motor and non-motor systems. It not only affects the adults but also children and teenagers. Early significant loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and extensive accumulation of alpha-synuclein (aSyn), an intracellular protein, are hallmarks of Parkinson's disease (PD).

The causes of Parkinson's disease are unknown for most of the parts. In recent years, genetic risk factors have been discovered. When compared to the general population or controls, first-degree family members of affected individuals have a 2- to 3-fold greater risk of developing the condition. Slow voluntary movement initiation with an increasing reduction in speed and amplitude of repeating activities, along with muscle rigidity, resting tremor, or postural instability, are some of the symptoms of PD.

Molecular Events Underlying PD

With an average beginning age of 50 to 60 years, ageing is the most powerful risk factor for PD. From a pathological perspective, common issues seen in Parkinson's disease

patients, such as depigmentation, neuronal demise, and gliosis, impact both the pontine locus coeruleus and substantia nigra pars compacta. By the time PD symptoms appear, the substantia nigra pars compacta has lost 60–70 per cent of its neurons. Treatments for PD have ranged from different drugs to rehabilitation and even surgery, depending on the symptoms and demands of the individuals.

2. Method

2.1. Studying Molecular Docking

Being one of the most important tools in structural molecular biology and computer-assisted drug design, ligand-protein docking has the capability to anticipate the most frequently observed binding configuration(s) for a ligand when interacting with a protein of known three-dimensional structure. Efficient exploration of high-dimensional spaces and the utilization of accurate candidate docking ratings are key aspects of successful docking algorithms. Docking can be employed for virtual screening of extensive compound libraries, result assessment, and the generation of structural hypotheses regarding how ligands inhibit the target, offering invaluable assistance in lead optimization.

2.2. Selecting Protein

Since then, Parkinson's disease has been linked to degeneration of the brain's basal ganglia and a lack of the neurotransmitter dopamine. The most effective treatment for Parkinson's disease symptoms is levodopa. Dopamine receptors are a type of G-protein coupled receptor found in the brain and spinal cord. D1 like receptors include D1 and D5 receptors, which are involved in adenylate cyclase stimulation, while D2 like receptors include D2, D3, and D4 receptor subtypes, which are involved in adenylate cyclase inhibition.

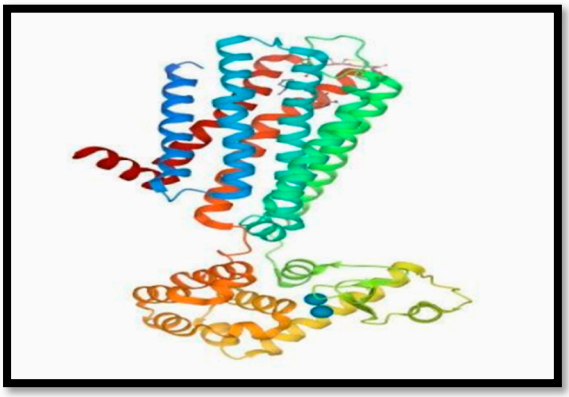


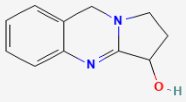
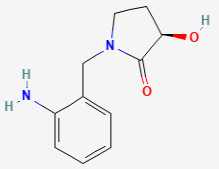
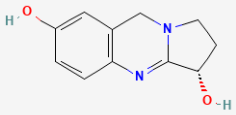
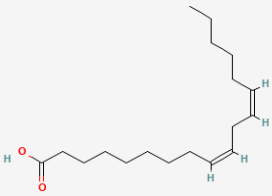
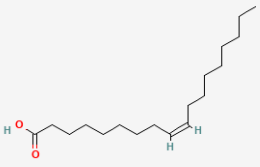
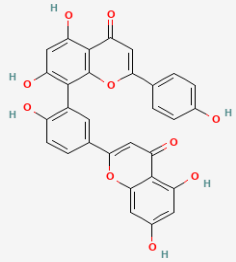
Figure 1. 3-D 3PBL-Structure of the human dopamine D3 receptor in complex with Eticlopride.

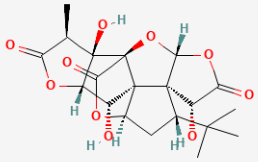
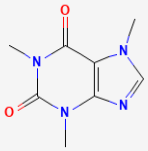
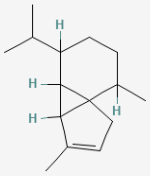
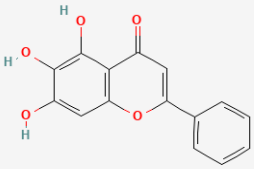
The crystallographic depiction of the human dopamine D3 receptor (D3R) in association with the D2R/D3R-specific antagonist Eticlopride offers crucial insights into the ligand binding pocket and the extracellular loops. Two unique conformations of the intracellular loop and the ionic lock's locked conformation are found on the intracellular side of the receptor. The extracellular expansion of the Eticlopride binding site revealed by docking R-22, a D3R-selective antagonist, includes another pocket of binding for R-22's aryl amide, which is in contrast to the very homologous D2R and D3R.

2.3. Selecting Phytoconstituents

Here 10 phytoconstituents have been used to study docking scores and results are compared with that of Levodopa in the treatment of Parkinson's disease.

Table 1. Phytoconstituents used in docking.

S. No.	Name	Active Phytoconstituents	Structure
1.	*Justicia adhatoda L.*	Vasicine	
2.	*Justicia adhatoda L.*	Vasicol	
3.	*Justicia adhatoda L.*	Vasicinol	
4.	*Justicia adhatoda L.*	Linoleic Acids	
5.	*Justicia adhatoda L.*	Oleic acids	
6.	*Ginkgo biloba L.*	Amentoflavone	

S. No.	Name	Active Phytoconstituents	Structure
7.	*Ginkgo biloba L.*	Ginkgolide B	
8.	*Coffea arabica L*	Caffeine	
9.	*Schisandra chinensis (Turcz.) Baill*	α-cubebene	
10.	*Scutellaria baicalensis*	Baicalein	

2.4. Docking

The FlexX docking software was used to perform a docking investigation of 10 phytoconstituents with 3PBL protein. FlexX, a quick and adaptable virtual screening docking software, makes use of pharmacophore restrictions, chemical series docking, and template docking. Docking allows for the prediction of the best ligand and the identification of the drug-receptor complex with the lowest free energy.

2.5. Comparing the Docking Scores of Levodopa in Contrast to That of the Mentioned Phytoconstituents

The parameters taken into consideration are:

(a) High Match: Low Match
(b) High Rank: Low Rank.
(c) Score

3. Results & Discussion

Pictures were taken from FlexX docking software to compare the results of each of the phytoconstituents with Levodopa. The protein structure however was extracted from RCBS Protein-Data Bank (PDB) with the PDB Id from the literature search. The result shows a comparison between energies obtained after docking Levodopa and Vasicol over 3PBL.

- Binding configuration and docking result of L dopa with 3UZA

Levodopa is most typically used as a dopamine replacement medication in the treatment of Parkinson's disease as it is a precursor to dopamine. It works well for controlling the bradykinetic symptoms that accompany Parkinson's disease.

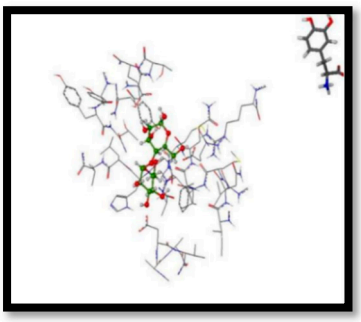


Figure 2. Levodopa docked on 3PBL receptor.

Table 2. Data from docking Levodopa on 3PBL receptor.

Pose Name	Rank	Score	Match	#Match
High-Rank	1	−23.1188	−28.5910	12
Low-Rank	293	−6.1107	−12.1814	6
High Match	1	−23.1188	−28.5910	12
Low Match	261	−8.0037	−14.8077	3

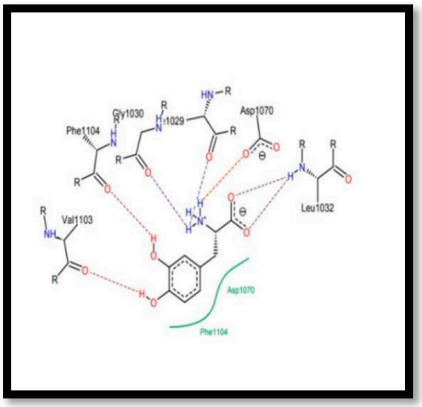


Figure 3. High Match-Levodopa docked on 3PBL receptor.

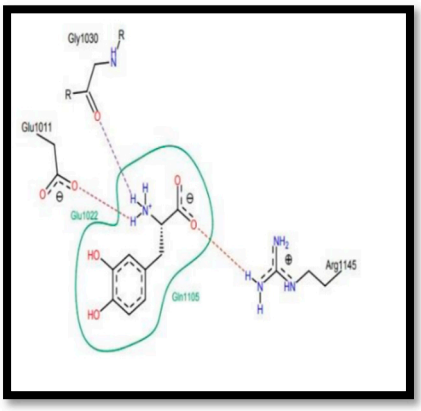


Figure 4. Low Match-Levodopa docked on 3PBL receptor.

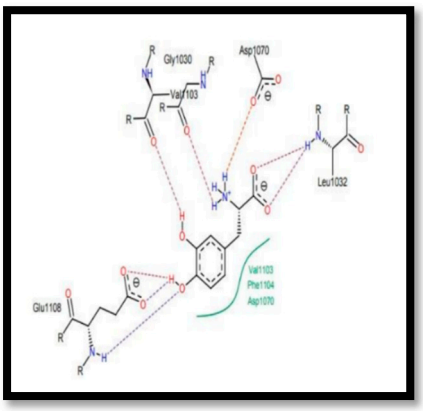


Figure 5. High Rank-Levodopa docked on 3PBL receptor.

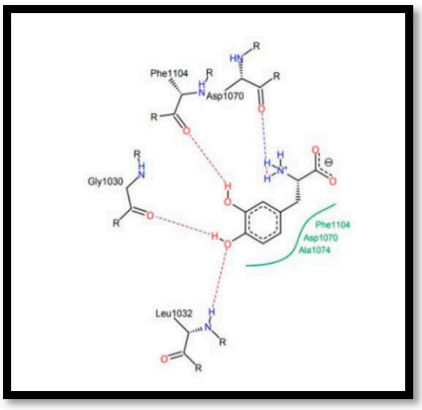


Figure 6. Low Rank-Levodopa docked on 3PBL receptor.

- Binding configuration and docking result of Vasicol with 3UZA

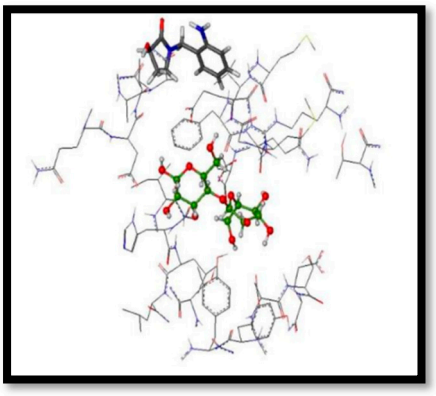


Figure 7. Vasicol docked on 3PBL.

Table 3. Data on docking of Vasicol on 3PBL.

Pose Name	Rank	Score	Match	#Match
High-Rank	1	−19.6871	−23.5103	8
Low-Rank	533	−4.8013	−8.2000	6
High Match	28	−12.9462	−14.1511	10
Low Match	457	−6.4538	−9.1826	2

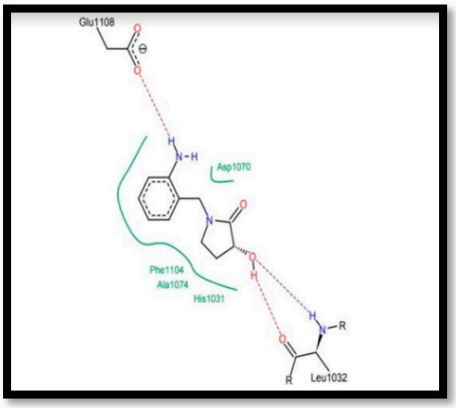


Figure 8. High Match- Vasicol docked on 3PBL.

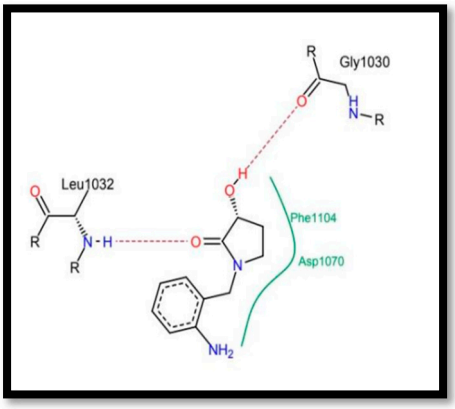


Figure 9. Low Match-Vasicol docked on 3PBL.

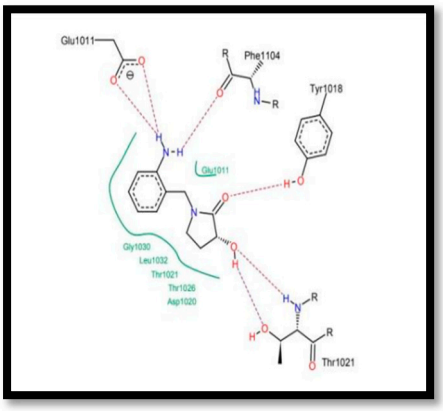


Figure 10. High Rank-Vasicol docked on 3PBL.

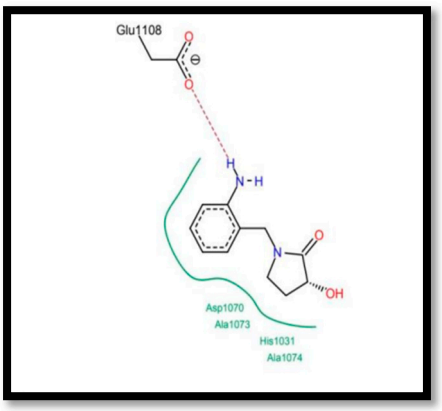


Figure 11. Low Rank-Vasicol docked on 3PBL.

Table 4. Comparison of docking energy in 3PBL.

Compound	Docking Energy
Levodopa	−23.1188
Vasicol	−19.6871
Caffeine	−10.5756
Amentoflavone	−16.7882
Alpha-cubebene	Not docked
Baicalein	−19.4789
Ginkgolide B	Not docked
Linoleic Acid	−3.6158
Oleic Acid	−2.2267
Vasicinol	−17.4828
Vasicine	−14.4955

The docking results show that all the plant compounds and Levodopa have their energy in negative value which suggests good binding on the chosen receptor.

- Levodopa, however, has the highest energy as compared to the chosen phytoconstituents.
- Vasicol has the closest energy value to that of Levodopa whereas Oleic Acid has the least energy value.
- We also see that Ginkgolide B and Alpha-cubebene shows no binding on 3PBL receptor.

4. Conclusions

Parkinson's disease is a movement illness that affects the nerve system. Tremors are common, however they are also associated with stiffness or slowed movement. Gene therapy, surgery, and drugs like Levodopa are some of the treatments available. However, Levodopa carries certain side effects like dizziness, loss of appetite, diarrhoea, dry mouth, etc. To overcome such effects, replacement of Levodopa with bioactive ingredients is performed to treat Parkinson's disease.

In this experiment, a d2/d3 receptor protein called 3PBL was selected to dock it with ten bioactive ingredients, each of which gave a unique result. The results were compared and it was ensured that certain phytoconstituents have similar binding energies to that of Levodopa. Out of the ten, Vasicol showed the closest energy value to that of Levodopa and is therefore capable of replacing Levodopa.

With the advancements in phytochemistry and medicinal chemistry, there is immense scope for the replacement of allopathic medicines with competent bioactive phytoconstituents. The good binding energy suggest better mechanism and lesser side effects in treatment to Parkinson's disease.

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