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In Silico Study of Natural Product Inhibitors of AChE and their Potential Therapeutic Value for the Cholinergic Hypothesis in the Development of Alzheimer's Disease

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Abstract: ***The most prevalent cause of dementia in elderly persons is Alzheimer's Disease (AD), which is characterized by a progressive deterioration in cognitive function as a result of brain damage. The cholinergic system anomalies are the most severely affected. As cholinergic deficits could be treated by reversibly inhibiting the acetylcholinesterase (AChE) enzyme, inhibition of AChE has become one of the most promising therapy options for AD. The main goal of this study is to investigate the natural product inhibitors of AChE and their potential therapeutic value for the cholinergic hypothesis in the development of AD using molecular docking approach. The crystal structure of hAChE; PDB entry: 6O4W was used in this study. Ten selected drug candidates including Ginsensoside, Apigenin, Curcumin, Mangiferin, Galantamine, Resveratrol, Rivastigmine, Ribalinine, Caranine, and tazettine were docked in order to determine their binding affinities using Avagadro, pYrX, and Discovery Studio 2019 Client software. The bioavailability of the drugs was assessed by using swissADME web server obtaining bioavailability radar and pharmacokinetics was evaluated using protox web server. Then their recent progress in drug development in relation to their properties was discussed in the study. According to the Binding affinities of the inhibitors Apigenin, Ginsensoside, Curcumin, and Caranine showed the highest potential for inhibitory activity respectively. The re docking results showed that the conformation of the docked ligand sufficiently matches with the original ligand; hence the docking protocol was validated.***

Keywords: cholinergic hypothesis, acetylcholinesterase (AChE) inhibitors, natural product inhibitors of AChE, molecular docking

1. Introduction

Alzheimer's disease (AD) is the most common causes of dementia in elderly people. It is characterized by low levels of acetylcholine in the brain of AD patients. According to the cholinergic hypothesis, the inhibition of acetylcholinesterase (AChE), an enzyme that catalyzes acetylcholine hydrolysis, increases the levels of acetylcholine in the brain, thus improving cholinergic functions in AD patients [1].

The Bavarian neuropsychiatrist Alois Alzheimer is the 1st person who described about the symptoms of "a particular disease of the cerebral cortex", characterized by a gradual and irreversible degeneration of the intellectual functions such as memory, orientation, judgment, language and the capacity to obtain new data, in1906, during the 37th Conference of German psychiatrists in Tübingen [2].

The early stages of the AD patients show the symptoms of forgetting recent events or conversations. As the disease progresses, a person with AD disease will develop severe memory impairment and lose the ability to do day today activities. The key symptom of AD is the memory loss. When the disease progress continuously memory impairment worsen and other symptoms will develop. As cholinergic deficits could be treated by reversibly inhibiting the acetylcholinesterase (AChE) enzyme, inhibition of AChE has become one of the most promising therapy options for AD [3].

The primary function of acetylcholinesterase (AChE) is to stop the transmission of nerve impulses at the cholinergic synapses through fast acetylcholine hydrolysis (ACh). AChE inhibition is a technique for the Alzheimer's disease treatment (AD). There are a few synthetic medications for treating cognitive dysfunction and memory loss related to AD, such as tacrine, donepezil, and the natural product-based rivastigmine [4]. Finding more effective AChE inhibitors from natural sources is necessary because these substances have been shown to have side effects, such as gastrointestinal disturbances and issues with bioavailability [2].

Several AChE inhibitors are currently available for the symptomatic management of people with mild-to-moderate AD, including donepezil, galantamine, and rivastigmine. The main goal of this in silico study is to investigate the natural product inhibitors of AChE and their potential therapeutic value for the cholinergic hypothesis in the development of AD using molecular docking approach [5]-[7]. Ten selected drug candidates including Ginsensoside, Apigenin, Curcumin, Mangiferin, Galantamine, Resveratrol, Rivastigmine, Ribalinine, Caranine, and tazettine were used for the docking process and their binding affinities, pharmacokinetics, bioavailability, and druglikeliness properties were discussed as in silico study [8],[9].

2. Methodology

2.1 Preparation of the Protein

Three dimensional crystal structure of binary complex of native hAChE with donepezil (PDB ID: 6O4W) was

obtained from protein data Bank (https://www.rcsb.org/) which is shown in Fig.1. Then the mentioned PDB file was loaded into notepad++ for molecular docking preparation. The docked ligand was determined and the active site for the particular ligand was identified using notepad++. The file was edited such that only the chain A is remained. Then the file was saved under an appropriate name as a PBD file.

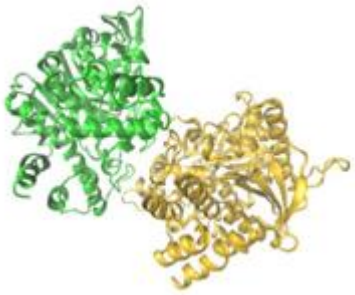

Figure 1: Three dimensional crystal structure of binary complex of native hAChE with donepezil

2.2 Preparation of ligands

The compounds were sketched and energy optimization was done using avogadro software. The MMFF94s force field and conjugate gradient algorithm were used for optimization. The energy was minimized for each compound for 100 steps. The minimized compounds were then saved as PDB files with appropriate names. Sketched ligands were given from Fig. 2 to Fig. 11.

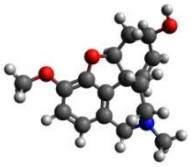

Figure 2: Galantamine

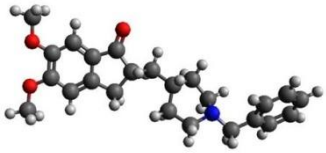

Figure 3: Donepezil

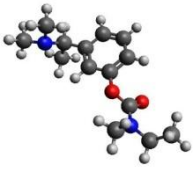

Figure 4: Revastigmine

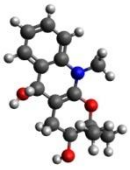

Figure 5: Rebalinine

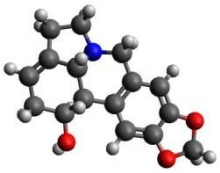

Figure 6: Caranine

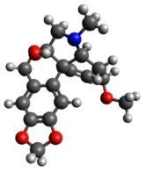

Figure 7: Tazetine

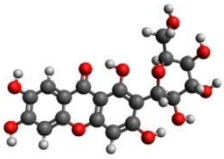

Figure 8: Mangiferin

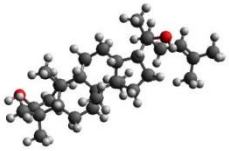

Figure 9: Ginsen

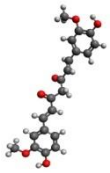

Figure 10: Curcumin

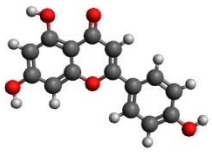

Figure 11: Apigenin

2.3 Molecular docking using PyRx software

The saved PDB files and the edited protein file were loaded into the PyRx software. The protein was made as a macromolecule and the compounds sketched from Avogadro were made as ligands. Then vina vizard was run. The active site residues were selected using the "Toggle" icon and the grid box which is given in Fig. 12 were adjusted around the active site residues of the protein. Docking was carried out using autodock vina. The docked poses and the binding energies of all the docked poses were exported from PyRx. The best docking pose of each ligands were analyzed and 2-D and 3-D interaction diagrams were obtained from BIOVIA Discovery Studio 2019 Client.

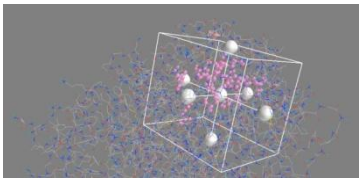

Figure 12: Adusted grid box in PyRx

2.4 Prediction of ADME parameters and pharmacokinetic properties

SwissADME server (http://www.swissadme.ch/index.php) was used to assess the adsorption, distribution, metabolism and excretion properties of the ten ligands. The canonical smiles of the natural product drugs were obtained from pub chem (https://pubchem.ncbi.nlm.nih.gov/) website. The bioavailability radar diagrams and the boiled egg diagram thus obtained were recorded.

3. Results and Discussion

3.1 Binding affinity results obtained from PyRx

Table 1 displays the binding affinity results of the ligands with 6O4W. The values of the highest binding affinity for each ligand were given in this table and the modes of with the highest binding affinity were used for the docking process.

Table 1: Binding affinity results

Ligand	Binding affinity/ kcal mol^{-1}
galantamine	-9.1
caranine	-9.5
tazettine	-9.2
mangiferin	-9.2
rivastigmine	-8.1
caranine	-9.5
ginsenosides	-9.9
ribalinine	-8.9
apigenin	-10.0
resveratrol	-9.3
curcumin	-10.3

3.2 Re docking results

The 2D interaction diagrams obtained for the original and docked donepezil ligand in complex with 6O4W is displayed in Fig. 13 and 14. The redocking results showed that the conformation of the docked ligand sufficiently matches with the original ligand; hence the docking protocol was validated.

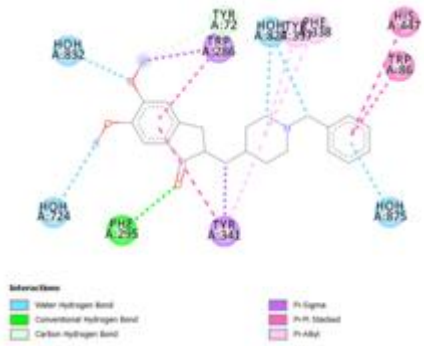

Figure 13: Interaction diagram of re docked ligand

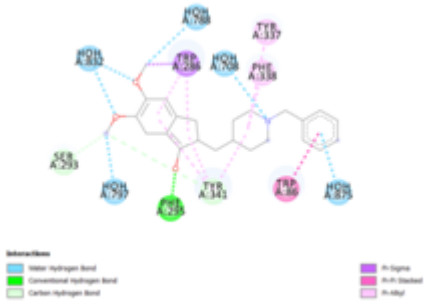

Figure 14: Interaction diagram of original ligand

3.3 Molecular docking

Molecular docking process was done using the discovery studio software. The 2D ligand interaction diagram for the ligands with highest binding affinities other than Donepezil was shown in Fig. 18 and 19.

3.4 Pharmacokinetics and drug likeliness property assessment

According to the data obtain form the swissadme pharmacokinetics study it is observed that all the selected drugs has potential bio availability on the AChE inhibitory activity. The bio availability radar diagrams of donepezil, galantamine and rivastigmine are shown in Fig.15, 16 and 17.

Figure 15: Bioavailability radar of donepezil

Figure 16: Bioavailability of galantamine

Figure 17: Bioavailability of rivastigmine

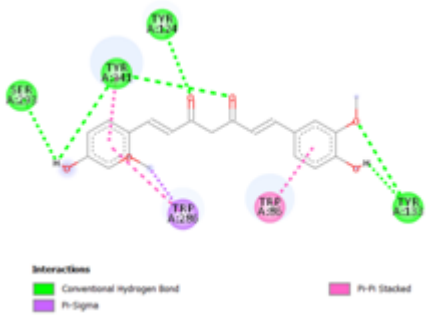

Figure 18: 2D ligand interaction diagram of curcumin

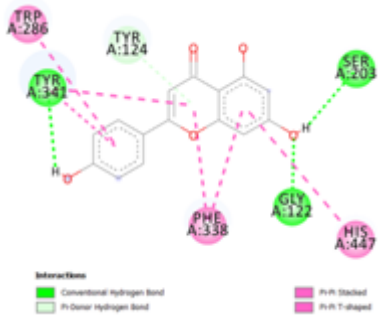

Figure 19: 2D ligand interaction diagram of apigenin

4. Conclusion

In this in study, ten selected drug candidates including ginsensoside, apigenin, curcumin, mangiferin, galantamine, resveratrol, rivastigmine, ribalinine, caranine, and tazettine were docked in order to determine their binding affinities with the crystal structure of hAChE; PDB entry: 6O4W. According to the obtained bioavailability radar diagrams from the Pharmacokinetic and druglikeliness properties assessment, indicated that all the selected drugs are suitable for the docking process. The re docking results showed that the conformation of the docked ligand sufficiently matches with the original ligand; hence the docking protocol was validate. Then their recent progress in drug development in relation to their properties was discussed in the study. According to the Binding affinities of the inhibitors Apigenin, Ginsensoside, Curcumin and Caranine showed the highest potential for inhibitory activity respectively. But applicability of these compounds in practice requires further research.

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