Comparative Molecular docking studies on natural compounds and a commercial drug against Acetylcholinesterase using iGEMDOCK

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Abstract:

Alzheimer's disease (AD) is an irreversible neurodegenerative disease caused by the conversion of Acetylcholine (ACh) an organic substance functioning as the neurotransmitter by the enzyme Acetylcholine esterase (AchE). This disease is managed by administering the drugs which inhibit the acetyl choline esterase. However the side effects of these drugs are unavoidable when they used for longer time. Nowadays scientists are looking for natural compounds to cure the disease with minimum side effects. The molecular docking is a method that can predict the most favourable orientation of a molecule (ligand) when interacting with a macromolecular target like an enzyme or protein which form a stable complex. The most important thermodynamic parameter in this method is the binding free energy.In this work, the natural compounds like Quercetin, Luteolin, Kaemperol which are AChE inhibitors were docked against Acetylcholinesterase (PDB ID: 1EVE). Donepezil was used as the reference to compare the binding energy. Docking software iGEMDOCK was used to dock the protein 1EVE with the drug compounds. AChE protein (IEVE) protein was docked with the compounds like Quercetin, Luteolin, Kaemperol and Donepezil using iGEMDOCK software.The analysis of docking score and energy showed that the Donepezil (-120.46) showed the best results than other ligands like luteoline (-111.96), kaemferol(-115.57) and quercetin (-115.85). However the binding energy of all the three natural compounds could be used as the lead compounds their derivatives could be screened for better results.

Keywords: Alzheimer's disease (AD), Acetylcholinesterase, iGEMDOCK, Quercetin, Luteolin, Kaemperol and Donepezil

Introduction:

Alzheimer's disease (AD) is an irreversible neurodegenerative disease of brain neurons. The term Alzheimer's was first used by the German physician Alois Alzheimer in 1906 (Singhal *et al*., 2012). Acetylcholine (ACh) is an organic substance functioning as the neurotransmitter which is involved in the transfer of neuronal signals in the brain. Acetylcholine esterase (AchE) is an enzyme converting acetylcholine into choline and acetate (GladiesKezia *et al*., 2013). When the concentration of Acetylcholine goes down, it leads to a neurological disorder resulting in Alzheimer's diseases. It is estimated that approximately 25 million people worldwide have been affected with this disease. The inhibition of the enzyme acetyl choline esterase (AChE) increases the levels of the neurotransmitter acetylcholine and symptomatically improves the affected cognitive function (Doytchinova *et al*., 2018). The drugs such as huperzine A, galanthamine, rivastigmine, galantamine and donepezil are available in the market as AChE inhibitors. Currently, people are looking forward for plant-based drugs for their health needs because these drugs are believed to have fewer side effects. Mostly the individuals taking crude extracts are doing so without knowing the scientific background (Vijayakumar *et al*., 2017). A lot of bioactive compounds have been isolated and characterized in the recent past which are believed to be the bioactive principles behind the medicinal property of the plants. A more elaborative throughput study is the need of the hour which will shed more light on the principle behind the molecular interactions.

The molecular docking is a method that can predict the most favourable orientation of a molecule (ligand) when interacting with a macromolecular target like an enzyme or protein which form a stable complex. The most important thermodynamic parameter in this method is the binding free energy ($\Delta G_{binding}$), which provides us the theoretical stability of the ligand-protein complex (Kitchen *et al*., 2004). It is used to reveal the orientation of one molecule to another in which they bound to each other to form a stable complex compound (Mohan *et al*., 2005 and Kitchen *et al*., 2004)

In this work, the natural compounds like Quercetin, Luteolin, Kaemperol were docked against Acetylcholinesterase (PDB ID: 1EVE). Donepezil was used as the reference to compare the binding energy.

Materials and methods:

Preparation of the target protein structure: The protein Acetylcholine esterase (PDB ID: 1EVE) was procured from protein data bank (pdb), a repository for 3-D structure of protein molecules (https://www.rcsb.org/)

Preparation of ligands: The natural compounds such as Quercetin, Luteolin, Kaemperol (Figure 1a-1c)were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) database. The standard drug, Donepezil (figure 1d) also was obtained from the database. All the above four compounds were downloaded in downloaded in (.sdf) format and they were converted into (.pdb) format by using OpenBabel[7] (http://openbabel.org/)software.

Figure 1.Structure of compounds used as ligands

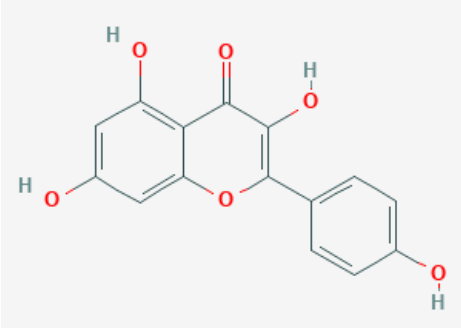


Figure 1a. Kaempferol

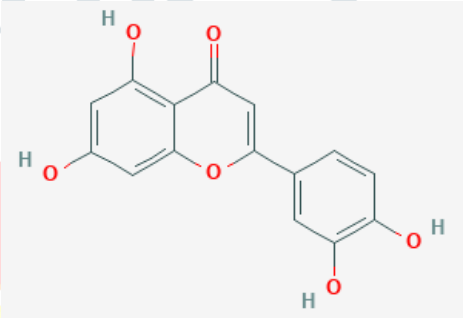


Figure 1b. Luteolin

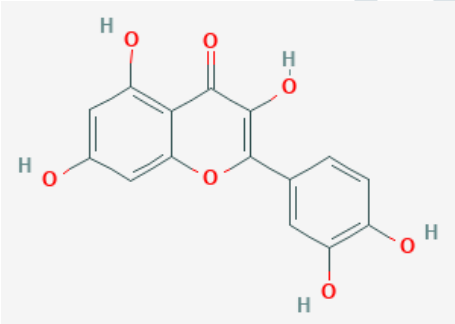


Figure 1c .Quercetin

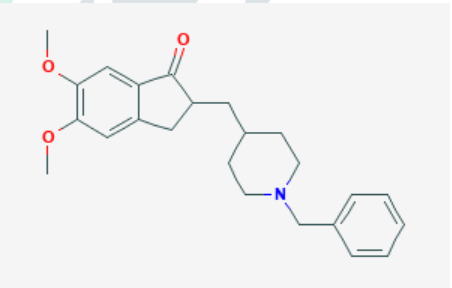


Figure 1d. Donepezil

Docking module: Docking software iGEMDOCK[8] was used to dock the protein 1EVE with all the ligands. This docking software uses the generic evolutionary method for molecular docking. It is a automatic graphical interface used for docking, screening and post-screening analysis of the docked molecules.

iGEMDOCK provides an easier interactive interfaces to prepare the binding site of the target protein and the compounds in the library. Each compound in the library is then docked into the binding site separately. Finally, iGEMDOCK generates protein-compound interaction profiles of electrostatic (E), hydrogen-bonding (H), and Van der Waal's (V) interactions; it ranks and visualizes the screening compounds by combining the pharmacological interactions and energy-based scoring function of iGEMDOCK.

Results and discussion:

AChE protein (IEVE) protein was docked with the compounds like Quercetin, Luteolin, Kaemperol and Donepezil using iGEMDOCK software and the docked scores of those molecules were represented with their binding energy, Vanderwaal energy, electrostatic and hydrogen bond profiles (the images of docked poses are given in the figures 2a-2d) . Binding energies of the protein-ligand (drug) interactions are important to describe how fit the drug binds to the target macromolecule. From the analysis of docking score and energy, the Donepezil (-120.46) showed the best results than other ligands like luteoline (-111.96), kaemferol(-115.57) and quercetin (-115.85). While molecular interaction profile showed that the amino acids like Try-84, Phe-330, Phe-331, Tyr-334 and Gly-335 were engaged in the binding with the Donepezil, all the remaining compounds showed a different profile of interacting amino acids.

Even though maximum binding energy was observed with the drug Donepezil, the binding energy of all the three natural compounds were found to be very close to that of the drug. This shows that these compounds could be taken as the lead compounds from which more effective and safe drugs could be developed in future by lead optimization.

Figure 2. Print screens of best docked poses

Fig 2a:Protein 1EVE complexed with Quercetin

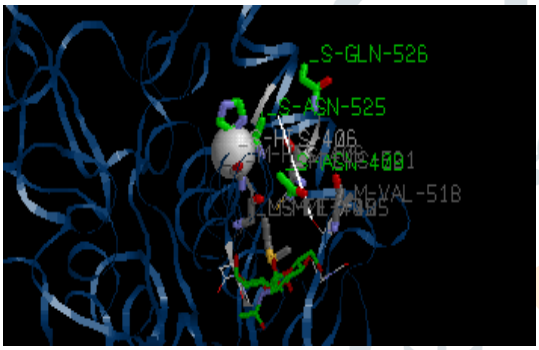


Fig2b:Protein 1EVE complexed with Luteolin

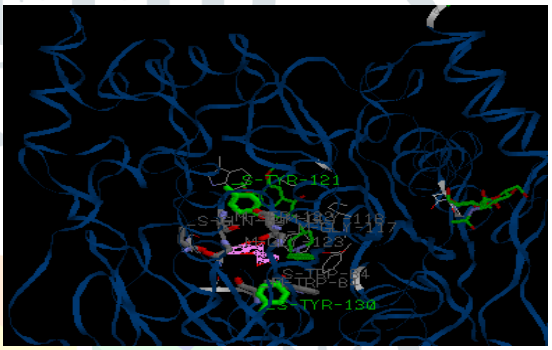


Fig 2c:Protein 1EVE complexed with Kaemferol

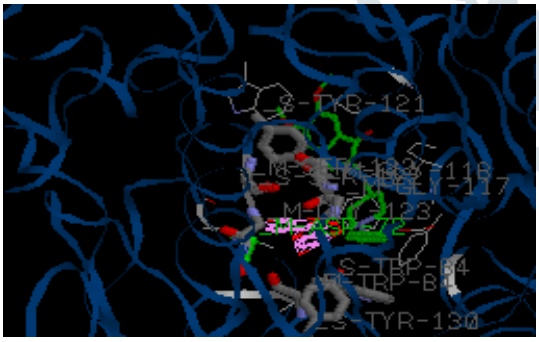
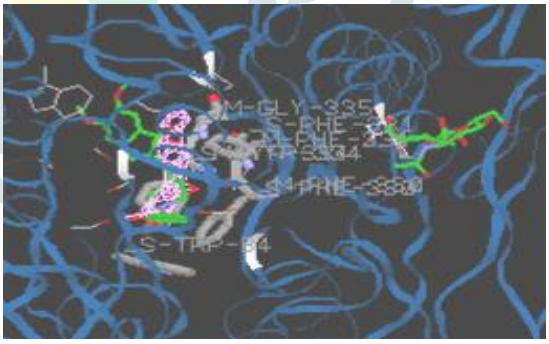


Fig 2d:Protein 1EVE complexed with Donepezil



Conclusion:

The molecular docking studies using the docking software iGEMDOCK showed that the natural compounds could be used as the lead compounds in developing drugs to manage Alzheimer's disease (AD). The binding energy of all the three natural compounds screen were marginally less than that of the standard drug, the results encourage to screen more and more natural compounds and subsequent development of drugs by lead optimization in future

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