IN-SILICO COMPARISON OF NATURAL COMPOUND AND SYNTHETIC COMPOUND TOWARDS ALZHEIMER'S DISEASE

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Abstract

The study on inhibition of Harmine, Tau protein, BACE-1 and Cholinesterase are the important approach for Alzheimer's diseases (AD) treatment. In this study, the inhibition target for the Alzheimer's diseases such as Harmine, Tau protein, BACE-1 Cholinesterase using synthetic and natural inhibitors were studied. Synthetic compounds such as Donepezil, Galantamine, Rivastigmine, Memantine and natural compounds such as Andrographolide, Artemisinin, Curcumin and Rosmarinic acid were used in this study. The purpose of this study is to identify the molecular interactions and differentiate the interactions between natural and synthetic compounds towards Harmine, Tau protein, BACE-1, and Cholinesterase. In this study, molecular docking method was used to identify the compound that has best interaction energy towards Harmine, Tau protein, BACE-1, and Cholinesterase protein target. In structure-based drug design, molecular docking method is used because of their ability to predict the binding-conformation of small-molecule ligands to the target binding site as the main objective of molecular docking is to attain a ligand- receptor complex with optimized conformation and with the intention of processing less binding free energy. The results obtained from the docking using Autodock Vina software showed the best affinity binding for the complexes Curcumin-Harmine, Artemisinin-Tau protein, Andrographolide-BACE-1, Rosmarinic acid-Cholinesterase. The molecular interaction analysis was then further observed using Discovery Studio Visualizer. It is hoped that this preliminary study can create new discoveries to find potential inhibitors for Alzheimer's diseases (AD).

Keywords: Alzheimer; Harmine enzyme, Tau protein enzyme, Bace-1 enzyme, Cholinesterase enzyme, synthetic molecule, Donepezil, Galantamine, Rivastigmine, Memantine, natural molecule, Gallic acid, Andrographolide, Artemisinin, Curcumin, Rosmarinic acid

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1. Background of Study

1.1 Introduction

Alzheimer's Disease is the most common cause of dementia, a general term for memory loss, and other cognitive abilities that are serious enough to interfere with daily life. Alzheimer's disease accounts for 60-80 percent of cases of dementia [1]. Alzheimer's is not a normal part of the ageing process. The greatest known risk factor is an increase in age and most people with Alzheimer's are 65 years of age and older. But Alzheimer's is not just an old-age illness. Alzheimer's has worsened over time. It is a progressive disease in which symptoms of dementia have gradually worsened over several years. In its early stages, memory loss is mild, but with late-stage Alzheimer's, individuals lose the ability to engage in conversation and respond to their environment. Someone with Alzheimer's lives on average four to eight years after diagnosis, but can live for as long as 20 years, depending on other factors [2].

This disease has no current cure, but symptoms treatment is available, and research continues. Although current treatments cannot stop Alzheimer's from progressing, they can temporarily slow down the worsening symptoms of dementia and improve the quality of life for people with Alzheimer's disease and their caretakers. Currently, there are five prescription drugs approved by the U.S Food and Drug Administrations (FDA) which can help with the symptoms. Donepezil, Galantamine and Rivastigmine are three of five synthetic compounds available and categorized as "Cholinesterase Inhibitors" [3] as shown in figure 1.1.1. These synthetic compounds prevent the breakdown of a chemical messenger in the brain that is important for learning and memory. The fourth prescription is memantine, it regulates the activity of another chemical messenger in the brain which is also important for learning and memory. [4] Both types of Alzheimer's Inhibitor help control symptoms, but they work in a variety of ways. The fifth medicine is a combination of one of the inhibitors of cholinesterase (donepezil) and memantine [3].

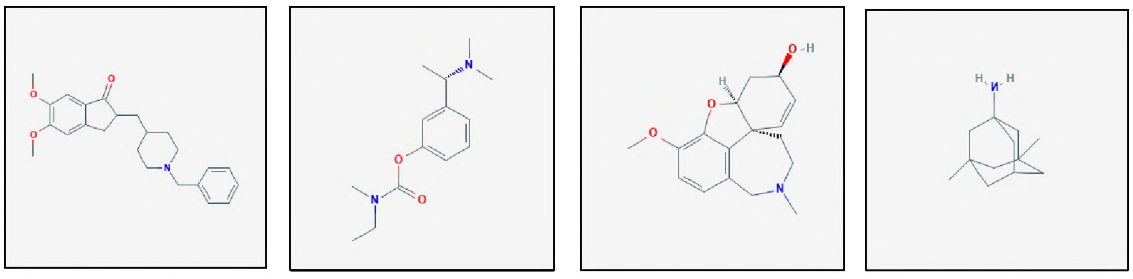
Cholinesterase inhibitors are prescribed for the treatment of symptoms related to memory, thinking, language, judgement, and other thought processes. Donepezil is used to treat all stages of Alzheimer's Disease [5], Galantamine for mild to moderate stages and Rivastigmine for mild-to-moderate Alzheimer's disease and mild-to-moderate dementia associated with Parkinson's disease [6]. Cholinesterase inhibitors work by increasing the level of acetylcholine, a chemical messenger involved in memory, judgement, and other thought processes [4]. Certain brain cells release acetylcholine, which helps to send messages to other cells. After a message reaches the receiving cell, different other chemicals, including an enzyme called acetylcholinesterase, break down acetylcholine so that it can be recycled. Alzheimer's disease damages and destroys cells that produce and use acetylcholine, reducing the amount of information available to carry messages. The cholinesterase inhibitor slows down the breakdown of acetylcholine by blocking the activity of acetylcholinesterase. By maintaining the level of acetylcholine, the drug may help compensate for the loss of functioning brain cells. Cholinesterase inhibitors also appear to offer other benefits. Cholinesterase inhibitors cannot reverse Alzheimer's disease and will not stop the underlying destruction of the nerve cells. As a result, their ability to improve symptoms eventually

decreases as brain cell damage progresses.

In clinical trials, it has been proven that people who taking the cholinesterase inhibitors performed better in memory and thinking tests than those taking placebo or inactive medications [4]. The efficacy of cholinesterase inhibitors and how long they are effective vary from person to person. Cholinesterase inhibitors have generally been well tolerated. If side effects occur, they usually include vomiting, nausea, increased frequency of bowel movements and loss of appetite. It is strongly recommended that the physician experienced in the use of these prescription medications monitor patients who are taking them and that the recommended guidelines be strictly followed.

Other than Cholinesterase Inhibitors, there is memantine that is also being used in improving memory, attention, reason language and the ability to perform simple tasks by people with Alzheimer's Disease. It was the first NMDA type antagonist Alzheimer's medication approved in the United States. It is used for the treatment of moderate to severe Alzheimer's disease. In 2005, the FDA declined to approve memantine for mild Alzheimer's disease. Memantine works by regulating the activity of glutamate, a chemical involved in the processing, storage, and recovery of information. Glutamate plays a major role in learning and memory by triggering NMDA receptors to allow a controlled amount of calcium to enter the nerve cell. Calcium helps to create the chemical environment needed for the storage of information. Overproduction of glutamate, on the other hand will overstimulates NMDA receptors to allow too much calcium in the nerve cells. This leads to cell disruption and cell death.

A clinical study found that people taking memantine showed a small but statistically significant improvement in their mental function and ability to perform daily activities. However, the study participants with the lowest cognitive function showed no improvement i n either daily activities or overall function. Just like other prescription medication, memantine has adverse side effects including constipation, confusion, headache, and dizziness.



Donepezil Rivastigmine Galantamine Memantine

Figure 1.1.1: Chemical Structure of Synthetic Compounds

The natural compounds used in this study are Rosmarinic Acid, Curcumin, Andrographolide and Artemisinin as shown in Figure 1.12. Rosmarinic acid is also a caffeic acid ester and a part of many members of the Lamiacea family, including Rosmarinus officinalis[7], which has antioxidant and anti-inflammatory impact. Recently has been shown to protect the neurons from in vitro oxygen-