UNIVERSITI TEKNOLOGI MARA
Cawangan Terengganu
Kampus Bukit Besi

CHE365 FINAL YEAR PROJECT (FYP)

INDIVIDUAL REPORT

Topic:

A STUDY OF AMENTOFLAVONE AND ITS DERIVATIVES TOWARDS HUMAN LYSOSOMAL ACID-ALPHA-GLUCOSIDASE (GAA) - POMPE DISEASE ON ITS BINDING AFFINITY AND MOLECULAR INTERACTIONS

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Abstract

Human lysosomal acid alpha glucosidase is the protein that contains the enzyme responsible for breaking down glycogen into glucose in the lysosomes. As glucose is the body's primary source of energy, especially for the muscles, the role of the human lysosomal acid alpha glucosidase is important as it breaks down the huge amount of glycogen consumed by humans. However, problems arise when there is a mutation in the acid alpha glucosidase gene (4). This mutation prevents the production of the needed amount of acid alpha glucosidase enzyme that is needed to break down the glycogen (4). This causes buildup of glycogen in human cells, which causes damage to organs and tissues. The main issue with Pompe disease is that it does not have a cure and due to the small number of cases it is not often placed as a priority (7). There are many proposed treatment methods, but for this research, the method used will be ligand-targeting therapy. The way it works is that by specifically attaching a ligand to the human lysosomal acid alpha glucosidase by molecular docking, we can enhance its binding affinity so that it can create more amounts of enzymes in the human lysosomes which will lead to more efficient and higher rate of glycogen breakdown. To find the appropriate ligand for this method, six different ligands were used for this simulation which are Amentoflavone, Bilobetin, Heveaflavone, Isoginkgetin, Putraflavone and Sequoiaflavone. To measure the effectiveness of each ligand, they are subjected to a binding affinity test to find the ligand with the lowest binding affinity and molecular interactions test to find out their interactions when bound to the human lysosomal acid alpha glucosidase. Using AMDock to find the appropriate value of binding affinity, while there wasn't a significant difference between each of the ligands, Amentoflavone has the lowest binding affinity at-9.3 and the best molecular interactions as they pose the most amounts of conventional hydrogen bond and pi-alkyl bond at three of each bond. The low value of binding affinity and the specific molecular interactions mentioned made it the most stable and effective ligand of all six that were researched. However, as this is only an online simulation, it is recommended to conduct physical research and testing to truly provide the most usable results.

1. Background of study

1.1 Introduction

Pompe disease is a rarely occuring disease that comes from the mutations of the acid alpha glucosidase (GAA) gene in human tissues (4). This mutation causes the inability to break down glycogens into glucose, which leads to glycogen build up in the human lysosomes (4). This causes damage to the organs and tissues, especially the skeletal muscles which are life threatening if not treated appropriately.

While the current main treatment for Pompe disease is enzyme replacement therapy, it is not very effective due to its limitations such as the poor targeting of enzymes and the unusual burden of the treatment which requires a lot of dosages which can be uncomfortable for the patients and the unwanted complications the treatment brings. Instead of using enzyme replacement therapy, for this research the method used will be the ligand targeting therapy instead where the ligand is targeted at proteins that produce the acid alpha glucosidase enzyme to enhance its efficiency in breaking down glycogens into glucose. This method is much more efficient as it doesn't require high dosages and is accurate in targeting the protein that produces the enzyme. For this research, six ligands which are Amentoflavone, Bilobetin, Heveaflavone, Isoginkgetin, Putraflavone and Sequoiaflavone will be simulated. Using AMDock, the value of the binding affinity between the ligand and the molecules can be found, where the ligand with the lowest binding affinity will be regarded as efficient due to the stability brought by having lower binding affinity. Then, using BIOVIA Discovery Studio, molecular interactions between the ligand and the protein

1.1.1 Problem Background

The current main treatment method for Pompe disease, enzyme replacement therapy requires high dosage amounts and causes unwanted complications. This research aims to explore ligand-based therapy in the form of ligand targeting therapy as the alternative to enzyme replacement therapy. Using six ligand derivatives, the research attempts to enhance the process of breaking down glycogen by comparing the binding affinity and molecular interactions from the ligand, where the ligand that shows the most stable results will be considered as a viable option for the ligand targeting therapy.

1.1.2 Objective

The objective of this research project is divided into three:

1. To find the value of binding affinity between the human lysosomal acid-alpha glucosidase and the six different ligands by conducting a simulation of molecular docking using AMDock application.

2. To visualize the molecular interactions between the human lysosomal acid-alpha glucosidase and the six different ligands by conducting a molecular docking simulation using BIOVIA Discovery Studio

3. To assess the results of the binding affinity and molecular interactions obtained from simulations of molecular docking and designate the most optimal ligand by assessing the stability of the molecular docking.

1.1.3 Project Scope

The project covers the simulations of molecular docking using six different ligands that will be tested using computational programs. These programs include but are not limited to PyMOL, AMDock and BIOVIA Discovery Studio. Using these programs, two separate results will be obtained. They are the binding affinity and the molecular interactions between the protein and ligand when they are docked together. The six different ligands are derivatives of Amentoflavone. In alphabetical order, they are Amentoflavone, Bilobetin, Heveaflavone, Isoginkgetin, Putraflavone and Sequoiaflavone. After the data of binding affinity and molecular interactions are obtained, they will be assessed by the stability they provide to the molecular docking process. The ligand that is deemed to be most stable after comparison with the other ligands will be designated as the most optimal ligand for the molecular docking process involving the human lysosomal acid alpha glucosidase protein.