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TITLE:

MOLECULAR DOCKING OF POTENTIAL INHIBITORS OF CURCUMIN AND ITS DERIVATIVES TOWARDS PPAR GAMMA

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TABLE OF CONTENTS

ABSTRACT

Diabetes is a disease caused by high sugar intake. It is happening when someone's body is not reacting appropriately to the effects of insulin that function to regulate the blood sugar level by transferring it into the cells. In the article by Dr. Saiful Bahari Kassim, who is the Consultant Endocrinologist and Head of the Department of Endocrinology suggests that healthy lifestyle to control diabetes in someone's condition [1]. However, there are still needs for prescribed medicine to be consumed by diabetes-infected persons. Turmeric has been used in traditional medicine, which is traditional Chinese medicine that can be used for diabetes [2]. Recent research has shown that an active component of turmeric, curcumin, has anti-inflammatory, anti-cancer and antioxidant properties that have been proven to benefit in preventing and treating various diseases including cancer, autoimmune, cardiovascular, neurological and diabetes disease [3]. Nowadays, computational techniques are widely used for accelerating drug discovery and reducing the cost-effectiveness of laboratory screening experiments. In this study, molecular docking of three phytochemicals from turmeric was carried out against non-thiazolidinediones (nTZDs). The results revealed that some of the phytochemicals showed a better dock score compared to the curcumin. Based on the score, it is suggested that these compounds can be further studied for potential drugs against diabetes.

CHAPTER ONE: BACKGROUND

1.1 Introduction

Diabetes is a disease that occurs when your blood glucose, also called blood sugar, is too high. Your body uses glucose as its primary energy source. This disease cannot be directly transmitted, but it might involve transmission factors such as genetic predisposition, lifestyle and pregnancy-related changes in metabolism. On November 2024, WebMD, which is a health information service website, declared that United State (U.S.) ranks third globally for diabetes, especially for men [4]. Since 1990, the number of generations especially adults, who have been exposed to this has increased by more than quadrupled to over 800 million worldwide, according to [5]. The proteins that are related to this disease are varieties. The common protein that relates is Peroxisome Proliferator-Activated Receptor Gamma (PPARγ), where agonists for non-thiazolidinediones (nTZDs).

The World Health Organization (WHO) who is responsible for conducting surveillance of diabetes, makes agreements with a Resolution on strengthening prevention and control of diabetes [6]. The common drugs usually used are Pioglitazone and Rosiglitazone. These two drugs are currently licensed to the PPARγ for the management of hyperglycemia in Type 2 Diabetes Mellitus (T2DM) [7]. However, the improvement of this also depends on several factors such as body mass index (BMI), glucose levels in the body, the degree of insulin resistance and the extent of β-cell failure. Moreover, nTZDs benefit the parameters of cardiovascular health like lipids, blood pressure, inflammatory biomarkers, endothelial function and fibrinolytic activity.

A study done by Cooper and co-workers showed that the treatment and prevention of disease can be overcome with the use of herbal medicine [8]. Most of the diseases can be treated with natural compounds including diabetes mellitus. Turmeric (Curcuma longa) dried, thick rhizomes are frequently pulverised for use in food, medicine and cosmetics. Medicinally, the plant such as curcumin used to be as one of interventions in pre-diabetes to prevent the progression of T2DM with benefits and a safety profile.

Current method which is computational modelling techniques has been introduced as preliminary study to identify the target compound for diabetes. This computational approach can reduce time and cost compared to the wet-lab experiments for designing the drug. It is involving the technique of predicting the interaction between a small molecule, ligands and protein at the atomic level [9]. Molecular docking has been essential in many drugs developments, particularly for the virtual screening as potential medicinal compounds. Currently, the development in docking techniques is determined as natural substrates of an enzyme to estimate its binding affinity.

In the present study, molecular docking techniques were used to identify the ligand-receptor binding stability and the interaction of ligands with the protein.

1.2 Literature review

This literature review explains the protein studied together with natural compounds that are specific to the protein. It is also explains the binding site or protein and ligands that are analysed by using the computational method of molecular docking.

1.2.1 Protein of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ)

Peroxisome Proliferator- Activated Receptor Gamma (PPARγ) is a nuclear receptor that regulates the transcription of genes. It is important in regulating of insulin sensitivity, adipogenesis and glucose where it known as therapeutic targeted especially in diabetes treatment [10]. There are 3 primary functions of PPARγ which are glucose homeostasis that regulated the sensitivity of insulin in the human body, lipid metabolism where it controls the fatty acid and anti-inflammatory responses where it modulates the immune cell activity. Additionally, PPARγ functions as ligand-activated transcription factor. However, PPARγ increase insulin sensitivity by modulating metabolism of glucose where it can activate genes of the insulin-dependent glucose transporters such as GLUT-4 and GLUT-1 that has anti-inflammatory properties [11].

The protein structure 2Q5S is a structure of PPAR-γ bound to the partial agonist nTZD, where it related to islet amyloidosis pathogens that can cause type 2 diabetes mellitus (T2DM) [12]. Islet amyloid polypeptide (IAPP), also known as amylin plays a crucial role in maintaining energy by regulating metabolic parameters such as blood sugar level. Type 2 diabetes mellitus is happening when the high blood sugar level that can be as glucose leads to disorders of the immune system [13]. There are 2 possibilities that can cause T2DM. Either the pancreas does not produce enough insulin, or a malfunctioning hormone affect the movement of sugar into cells.

1.2.2 Binding site of the protein between the ligands

A binding site is a specific location on a molecule, typically a protein, where a small molecule known as a ligand, which can be a drug or natural substance, can attach. The binding site is usually located on the surface of protein and has a pocket-like shape that securely holds the ligands. Its dimensions, form and composition create a suitable fit for a certain molecule, just like a lock and key. Accurately defining the binding site in virtual screening and docking procedures is crucial, as it involves understanding known ligands areas and potential binding modes to avoid unexpected orientations.

There are 4 types of binding sites, which are DNA/RNA, active, allosteric and receptor binding sites. Protein that regulates transcription and genes are linked to DNA and RNA binding sites. Chemical reactions are facilitated by active sites, whereas allosteric site alter the function of proteins. For hormones, neurotransmitters, or medications to cause cellular reactions, receptor binding sites are necessary. These site, which function as agonists or antagonists, are essential for controlling metabolic processes and medication effects. In order to exactly fit into the target binding site, drugs are frequently made to resemble natural ligands. Researcher can create medications that block or activate particular processes by examining the binding location of proteins.