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In Silico Docking of Chemical Compounds from Roselle Calyces (*Hibiscus Sabdariffa* L.) as Antidiabetic

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Abstract: The research was conducted by in silico docking of protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) with Roselle Calyces (*Hibiscus sabdariffa* L.) chemical compounds. The objective research was to determine the activity of the active compounds from Roselle Calyces (*Hibiscus sabdariffa* L.) as a potential inhibitor for protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) by using in silico docking method. The research was conducted using chemical compounds Roselle Calyces (*Hibiscus sabdariffa* L.) and models of protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) downloaded via Protein Data Bank (PDB) with code 1KHB, then performed docking process using the PLANTS program, and then evaluated of the docking score as docking process results. Docking score as the docking results for Quercetin, Hibiscetin, Gossypetin, Protocatechuic Acid, and Metformin respectively are – 89.2883; – 85.6101; – 83.7724; – 70.9521; and – 64.9661. Result show that 4 of the Roselle Calyces (*Hibiscus sabdariffa* L.) chemical compounds (Quercetin, Hibiscetin, Gossypetin, Protocatechuic Acid) have the lower docking score and better potential as inhibitors of protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) than Metformin.
Key Words : Docking, In Silico, *Hibiscus Sabdariffa*, Antidiabetic, Phosphoenolpyruvat Carboxykinase, PLANTS Program

Introduction

Diabetes Mellitus is affecting disorder to people of all age groups worldwide. Many synthetic medicines available for type 2 diabetes mellitus in the market. However, there is a strong requirement for the development of better antidiabetes compounds sourced especially from natural sources like medicinal plants[1]]. Literature showed that flavonoids are good antidiabetic metabolites; alkaloids, have similarly been implicated in the antidiabetic activities of plant[2].

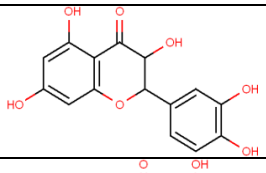
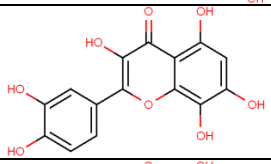
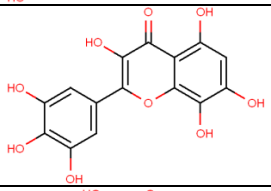
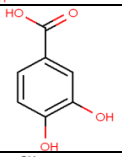
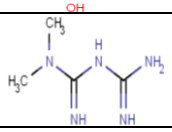
Roselle Calyces (*Hibiscus sabdariffa* L.) can treat many diseases and conditions (for example, diabetes and aging) are involve lipid peroxidation and the generation of free radicals[3]. Roselle Calyces (*Hibiscus sabdariffa* L.) contains flavonoids, such as: gossypetin, hibiscetin, and sabdaretin. Roselle Calyces (*Hibiscus sabdariffa* L.) also contains alkaloids, such as: protocatechuic acid, quercetin, anthocyanin, β-sitosterol, pectin, and wax[4]. The diet high in fructose and fat can cause insulin resistance, impaired glucose tolerance and hyperinsulinemia. These metabolic changes have been implicated as contributing factors to the development of type 2 diabetes mellitus. Investigation of antidiabetic efficacy of Roselle Calyces (*Hibiscus sabdariffa* L.) extract for type 2 diabetes mellitus examined by given extract of Roselle Calyces (*Hibiscus sabdariffa* L.) on high fructose and fat diet induced rats[5].

Protein Enzyme Phosphoenolpyruvate Carboxykinase (PEPCK) is expressed at high levels in liver, kidney, and adipose tissue. This enzyme catalyzes the rate limiting step in hepatic gluconeogenesis, renal gluconeogenesis, and adipose tissue glyceroneogenesis[6]. Therefore plays a central role in glucose homeostasis[7]. Binding site and coding regions of protein enzyme Phosphoenolpyruvate Carboxykinase (PEPCK) have been sequenced from cytosolic genomic Deoxy Nucleic Acid (DNA) of subjects with type 2 diabetes mellitus[8]. Protein enzyme Phosphoenolpyruvate Carboxykinase (PEPCK) contributes to the regulation of the triglyceride

cycle in adipose tissue and liver. Investigation of protein enzyme Phosphoenolpyruvate Carboxykinase (PEPCK) expression and its regulation in the triglyceride/fatty acid cycle is necessary for our understanding of maintenance of glucose homeostasis, lipid homeostasis, and disease prevention[9].

Metformin inhibits protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) gene expression either through the insulin independent pathway or an interacting with insulin manner[10]. Table 1 shows the chemical structure of Metformin and several Roselle Calyces (*Hibiscus sabdariffa* L.) chemical compounds.

Table 1.Chemical structure of Metformin and several Roselle Calyces (*Hibiscus sabdariffa* L.) chemical compounds.

Quercetin	
Hibiscetin	
Gossypetin	
Protocatechuic Acid	
Metformin	

Lead discovery was the main components of today's early pharmaceutical research. The aim of target discovery is the identification and validation of suitable drug targets for therapeutic intervention. Computational methods are being developed to predict the drug likeness of compounds. Thus, drug discovery is already on the road towards electronic Research & Development. In silico approaches contribute significantly to early pharmaceutical research and are especially important in target discovery and lead discovery. The need for timely adaptation and application of in silico approaches in pharmaceutical research has clearly been recognized and is expected to improve further the overall efficiency of drug discovery[11]. Therefore, there is an increased interest to identify potential activity of Roselle Calyces (*Hibiscus sabdariffa* L.) chemical compounds to protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) as the type 2 diabetes mellitus protein enzyme target compared with Metformin as the standard compound by in silico docking.

Material and Method

Model of the protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) was obtained through the Protein Data Bank (PDB) with the code 1KHB in the download RSCB (PDB) website (http://www.rcsb.org/pdb). Models of the Roselle Calyces (*Hibiscus sabdariffa* L.) chemical compounds (Quercetin, Hibiscetin, Gossypetin, Protocatechuic Acid) and Metformin made in the 2D and 3D formula structures by using the Marvin Sketch program. In silico docking used PLANTS program and visualized by Yasara program. Connector for Windows Operation System to Linux Operation System was done by Co Pendrive Linux KDE program.

Result and Discussion

GCP704 which was cocrystallized in the structure of 1KHB protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) was extracted and redocked into its original binding pockets. The Root Mean Square Deviation (RMSD) values resulted from these ligands redocking was 0.7757 Å, which was less than 2.0000 Å, a value typically used in evaluating the success of docking algorithms, indicating the docking methods was valid[12]. Figure 1 shows the redocking of GCP704 into the binding pocket 1KHB protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK).

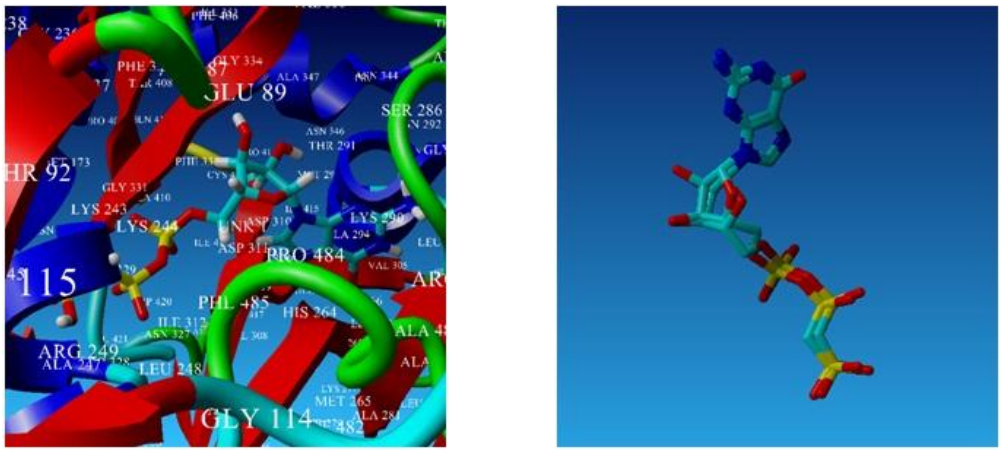


Figure 1. Redocking of GCP704 into the binding pocket 1KHB protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK).

In silico docking by PLANTS Program between protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) with Metformin as the standard compound and with Roselle Calyces (*Hibiscus sabdariffa* L.) chemical compounds (Quercetin, Hibiscetin, Gossypetin, Protocatechuic Acid) as the test compound resulting docking score. Table 2 shows docking result between ligand with the receptor protein enzyme Phosphoenol pyruvat Carboxykinase (PEPCK).

Table 2.Docking result between ligand with the receptor protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK).

Number	Ligand	Docking Score
1	Quercetin	– 89,2883
2	Hibiscetin	– 85,6101
3	Gossypetin	– 83,7724
4	Protocatechuic Acid	– 70,9521
5	Metformin	– 64,9661

Metformin as the standard compound which could inhibits protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) resulting higher docking score than Roselle Calyces (*Hibiscus sabdariffa* L.) chemical compounds (Quercetin, Hibiscetin, Gossypetin, Protocatechuic Acid) as the test compound. The docking score of the test compound with protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) is smaller than docking score of the standard compound. Docking score represents binding affinity of the ligand to the enzyme, smaller docking score value shows stronger interaction[13]. Quercetin has the smallest docking score and shows the strongest interaction to protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK). Figure 2 shows visualisation of interaction between Quercetin and protein enzim Phosphoenolpyruvat Carboxykinase (PEPCK).

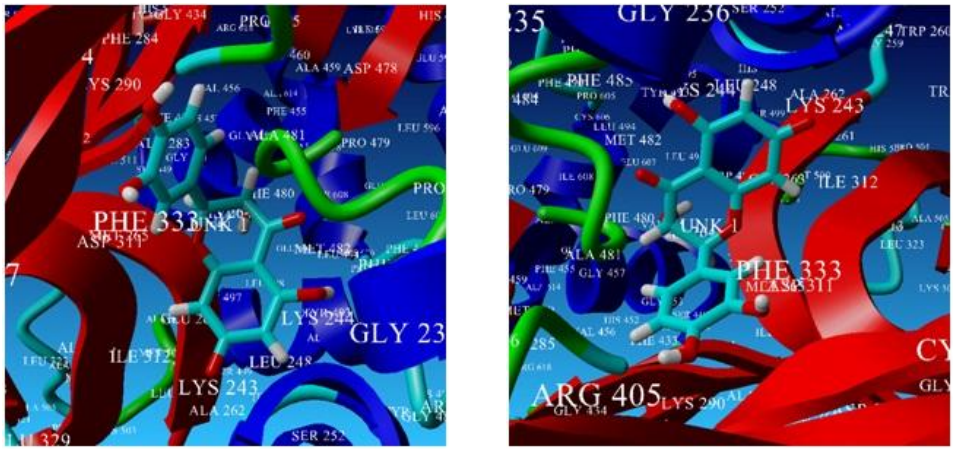


Figure 2. Visualisation of interaction between Quercetin and protein enzim Phosphoenolpyruvat Carboxykinase (PEPCK).

Conclusion

Result show that 4 of the Roselle Calyces (*Hibiscus sabdariffa* L.) chemical compounds (Quercetin, Hibiscetin, Gossypetin, Protocatechuic Acid) have the lower docking score and better potential as inhibitors of protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) than Metformin. Roselle Calyces (*Hibiscus sabdariffa* L.) chemical compounds with the lower docking score of bond means more stable and better for drug design because have the higher affinity.

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