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Anti-diabetic drug discovery using bioactive compounds: Molecular docking insights

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Abstract

Diabetes mellitus is a metabolic disorder that has become a global health problem. About 500 million people were estimated to be living with diabetes in 2018 with about 20 million in Africa and 2 million cases in Nigeria. Bioactive compounds offer an advanced starting point in the search for highly specific and potent modulator of bimolecular function as well as novel drugs, which can be studied with more precision by using computer aided drug design (CADD). Molecular docking employed for predicting the interactions between receptor and ligands is an integral aspect in drug discovery. The main objective is to attain ligand-receptor complex with optimized conformation and with the intention of possessing less binding free energy.

Several studies have used this method to explore the potency of bioactive compounds to predict better alternatives in the search for an anti-diabetic drug with very effective therapeutic role and minimal side effects. This has been carried out by using several compounds such as Quercetin, against endogenous targets such as Glycogen phosphorylase, Peroxisome Proliferator-activated Receptor (PPAR)- γ , Glucokinase, Protein Tyrosine Phosphatase 1-beta (PTP-1B), GLUT4, etc. In Silico tools such as Protein Database (PDB), GenBank and softwares such as Autodock and modeller are of major importance to these studies.

The paper seeks to examine bioactive compounds basically quercetin that have been successfully identified through molecular docking and their molecular targets as well as recent advances in the use of molecular docking in the novel discovery and explanation of mechanisms of actions of some bioactive compounds in anti-diabetic drug discovery.

Keywords: Diabetes mellitus; Molecular Docking; Bioactive compounds; Quercetin; Computer-Aided Drug Discovery and Design (CADD).

1. Introduction

Diabetes Mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia. It was reported that 366 million people had DM in 2011, and by 2030 this number is estimated to almost around 552 million [1]. The menace of DM and the rapid increase in number of cases worldwide has led to a pool of research on its causes and treatments. No cure has yet been found for the disease; however, treatment modalities include improved lifestyle changes, orally administered hypoglycemic agents, and use of metformin (an insulin sensitizer) [2]. Several studies have been carried out *in vivo* using bioactive compounds in natural plants (such as quercetin and yohimbine) in a search for

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the cure to DM. Biochemical studies have revealed that these bioactive compounds through different mechanisms have various activities in the human body such as antioxidant and antidiabetic functions [3,4].

Computer-aided drug designs (CADD) are playing an increasing role in drug discovery and are critical in the cost-effective identification of promising drug candidates [5]. Molecular docking employed for predicting the interactions between receptor and ligands is an integral aspect in drug discovery. The main objective is to attain ligand-receptor complex with optimized conformation and with the intention of possessing less binding free energy.

2. Diabetes Mellitus (DM)

The etiology of DM can vary greatly but always include defects in either insulin secretion, response or both at some point in the course of the disease [6]. DM can be classified into four classes which are; type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types [7].

2.1. Causes of Diabetes Mellitus

DM is a chronic metabolic disorder which is either immune-mediated as seen in Type 1 diabetes, insulin resistance as in Type 2 Diabetes, gestational as observed in pregnancy or due to other factors such as infections, environment, genetic defects and certain drugs [6].

Insulin and insulin receptors play a key role in the etiology of all forms of DM. Insulin exhibits a multitude of effects in many tissues, with liver, muscle, and adipose tissue being the most important target organs for insulin action. The basic physiological function of insulin is promoting the synthesis of carbohydrates, proteins, lipids, and nucleic acids. Insulin functions in stimulation of transport of glucose across muscle and adipocyte cell membranes, hepatic glycogen synthesis regulation, and glycogenolysis and gluconeogenesis inhibition [8]. Hence impairment of insulin function or response leads to a myriad of metabolic aberrations.

2.2. Treatment

Oral hypoglycemics have been of help in the maintenance of blood glucose level in diabetics through distinct mechanisms [9]. Sulfonylureas and non-sulfonylureas ensure normal glycemia by stimulating endogenous insulin secretion; alpha-glucosidase inhibitors work by delaying absorption of saccharides in the gut while thiazolidinediones (TZDs) maintain normal glycemia by stimulating insulin sensitivity majorly by enhancing peripheral glucose removal, and suppressing glucose production by the liver. Metformin is another major drug used in the management of diabetes; it works by downregulating hepatic gluconeogenesis while at times also increasing peripheral glucose mobilization and disposal [10]. Type I diabetes mellitus patients also rely on synthetic insulin injection.

3. Molecular Docking Studies

Molecular docking uses specific algorithm to find the best ligand molecule that fits within the active site of a target molecule possessing best possible pose. This search algorithm utilizes an energy scoring function suggesting the ligand molecule with lowest binding energy has the highest affinity for receptor binding [11]. In the experiment reported by [12] all the selected ligand molecules- Aegeline, Gallic acid, Mangiferin and Quercetin interacted with the target molecule with -5.622 Kcal/mol, -6.213 Kcal/mol, - 6.191 Kcal/mol and -6.496 Kcal/mol binding energy respectively. Quercetin with the lowest binding energy has the highest affinity for GSK3B binding and the highest binding energy of Aegeline suggests lowest affinity of interaction with GSK3B. Aegeline formed hydrogen bonds with 3 amino acid residues (VAL135, PRO136 and ARG141) of the target molecule, Gallic acid formed 4 hydrogen bonds (2×ILE62, VAL135, ARG141), Mangiferin formed 6 hydrogen bonds (2×ASP200, ASP133, ASP181, LYS83, LYS183) and Quercetin formed again 4 hydrogen bonds (2×ASP200, ARG141, VAL135) as Gallic acid within the active site of GSK3B. Aegeline and Gallic acid each interacted with 6 residues within the binding pocket of the target molecules whereas Mangiferin and Quercetin interacted with 10 and 8 residues respectively.

3.1. Drug-likeness Property

Lipinski's rule of five provides indication about the solubility, bioavailability and permeability of the drug molecule of interest. This rule assists in the shift of phase I trial to phase II trial of an investigational new drug with the help of computational approach that reduces both time and cost of the experiment [13]. TPSA or topological polar surface area is again associated with absorption and permeability of the drug molecule. Any candidate with higher TSPA value often results in poor permeability in biological system. Furthermore, higher drug score and drug likeness score indicate the best possibility of a candidate molecule to have the all the physicochemical parameters within range.

Mangiferin showed the highest TSPA value (201.28) and Aegeline showed the lowest TSPA value (58.56). Gallic acid and Quercetin showed moderate level of TSPA value- 201.28 and 127.4 respectively. Quercetin exhibited better drug likeness score (1.6) and drug score (0.3) after Aegeline which exhibited likeness score of 2.0 and drug score of 0.83.

3.2. ADME/T Test

All the molecules are impermeable to blood brain barrier offering no chance to cause damage to brain. Every molecule showed high absorption ability in intestine and didn't show any indication of carcinogenicity. Only Gallic acid showed colorectal tissue permeability. Cytochrome P450 (CYP) family of enzymes play major roles in drug metabolism, excretion and drug-drug interaction. Inhibition of any of these enzymes may cause unusual effects like slow degradation rate of the drug molecule, accumulation in the body and slow excretion [14]. Aegeline and quercetin are potent inhibitors of CYP450 3A4 and again quercetin is another inhibitor of CYP450 1A2. Gallic acid and mangiferin are not any inhibitors of any type of cytochrome P450 enzyme. Only gallic acid showed high degree of biodegradability among all the ligand molecules. Mangiferin showed the possibility to induce mutation as it positively indicated AMES toxicity.

4. Conclusion

Thousands of plants in nature have been reported to have antidiabetic activity. They have different mode of actions and deploy their effects by variety of mechanisms [15]. Quercetin could be a great candidate of antidiabetic agent against type II diabetes since commercially available treatments are not cost effective and employs some other complications. Moreover, other molecules also performed well indicating their potentiality to be used as antidiabetic agent. A well designed and targeted research can help us finding a potent and natural source of antidiabetic agent. Hopefully, molecular docking studies will enable researchers discover potent antidiabetic agents involved in the novel pathways also explanation of mechanisms of actions of these bioactive compounds with an overall aim in propelling anti-diabetic drug discovery will be effective.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest among the authors

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