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(RESEARCH ARTICLE)

In silico molecular docking studies of some phytochemicals against peroxisome-proliferator activated receptor gamma (PPAR-γ)

Ahmed H. A [1 *] and Alkali I. Y. [2]

[1] *Department of Pharmacognosy and Ethno pharmacy, Faculty of Pharmaceutical Sciences, Usmanu Danfodiyo University, Sokoto- Nigeria.*
[2] *Department of Pharmacology and Toxicology, Usmanu Danfodiyo University, Sokoto- Nigeria.*

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Abstract

Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ) is a ligand-activated transcription factor and a member of the nuclear receptor superfamily that regulate the gene expression of proteins involved in glucose, lipid metabolism, adipocyte proliferation and differentiation and insulin sensitivity. Thiazolidinediones (TZDs) are one important class of synthetic agonists of PPAR-γ. TZDs are antidiabetic agents that target adipose tissue and improve insulin sensitivity, and they are currently being used in the treatment of type 2 diabetes. The study was carried out in order to discover new phytochemicals that have the ability to stimulate the PPAR-γ using molecular docking studies. AutoDock vina was used as molecular-docking tool in order to carry out the docking simulations. Nine phytochemicals namely plumbagin, quercetin, isovitexin, mangiferin, syringin, lupe-20-ene-3-one, purine 2, 6-dione, diosmetin and β sitosterol and pioglitazone a standard drug were docked against PPAR-γ using AutoDock vina and the results were analyzed using binding affinity. The results revealed that the compounds have significant binding affinity towards the PPAR-γ comparable to pioglitazone the standard drug. Based on the findings of this study these phytochemicals can serve as source of antidiabetic drugs via the mechanism of agonizing of PPAR-γ.

Keywords: Molecular docking; Phytochemicals; Pioglitazone; Peroxisome proliferator activated receptor gamma

1. Introduction

Diabetes mellitus is a metabolic disorder characterized by disturbances in carbohydrate, protein and lipid metabolism [1]. Currently, the treatment for type-2 diabetes relies mainly on a variety of approaches such as guanidine analogues (metformin), insulin sensitizers; sodium glucose transporter-2 (SGLT-2) inhibitors, glucagon like peptidase-1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-IV) inhibitors, which are all intended to reduce hyperglycemia. However, these therapies have significant mechanism-based side effects, such as weight gain and cardiovascular diseases [2]. Peroxisome Proliferator-Activated Receptor γ (PPAR-γ) is a ligand-activated transcription factor and a member of the nuclear receptor superfamily that plays an important role in adipogenesis and glucose homeostasis [3]. PPAR-γ is activated by polyunsaturated fatty acids and their metabolites. This transcription factor regulates the expression of adipocyte-specific genes [4]. Its function is therefore, essential in fat cell formation. PPAR-γ full agonists stimulate triglyceride storage and the differentiation of pre-adipocytes into adipocytes [3]. Thiazolidinediones (TZDs) such as rosiglitazone and pioglitazone are PPAR-γ full agonists that have been widely used in the treatment of type 2 Diabetes mellitus. Despite the beneficial effect of lowering blood glucose level, Thiazolidinediones (TZDs) induce various side effects. Therefore there is a need to search for new compounds with potent antidiabetic activity with fewer side effects [5, 6]. Other compounds with poor agonist activities for PPAR-γ, called PPAR-γ modulators or PPAR-γ partial agonists, retain very good antidiabetic effects without these undesired side effects [6]. Many conventional drugs have been derived from compounds in medicinal plants, such as metformin, an efficacious oral glucose-lowering agent developed

* Corresponding author
E-mail address: aliyuhameedahmed@gmail.com

from *Galega officinalis* for the treatment of diabetes [7]. Due to the biodiversity and large number of secondary metabolites, plants, animals, fungi, microorganisms and other natural resources have been a rich source in the search for new drugs [8, 9].

Recently, the use of computers to predict the binding of libraries of small molecules to known target structures has become an important component in the drug discovery process [10, 11].There is a wide range of software packages available for the conduct of molecular docking simulations like, Autodock, GOLD, FlexX [12]. AutoDock vina is the most recent version which has been widely used for virtual screening, due to its enhanced docking speed. Its default search function is based on Lamarckian Genetic Algorithm (LGA), a hybrid genetic algorithm with local optimization that uses a parameterized free-energy scoring function to estimate the binding energy. Each docking is comprised of multiple independent executions of LGA and a potential way to increase its performance is to parallelize the aspects for execution [13]. Protein–ligand or protein–protein docking plays an important role in predicting the orientation of the ligand when it is bound to a protein receptor or enzyme using shape and electrostatic interactions to quantify it. The van der Waals interactions also play an important role, in addition to Coulombic interactions and the formation of hydrogen bonds. The sum of all these interactions is approximated by a docking score, which represents potentiality of binding. In the simplest rigid-body systems, the ligand is searched in a six-dimensional rotational or translational space to fit in the binding site, which can serve as a lead compound for drug design [14]. Numerous phytochemicals have been reported to possess potent antidiabetic activity but their mechanism of action has not been elucidated. This study was carried out in order to discover potential PPAR-γ using in silico docking studies [15]

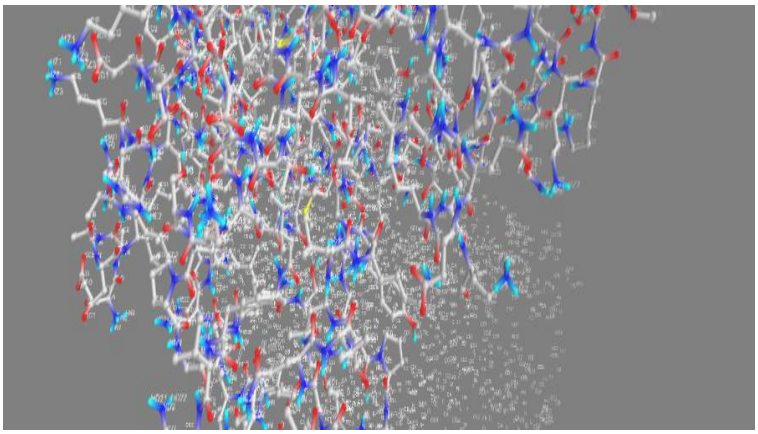

Figure 1 3D Structure of Peroxisome proliferator-activated receptor gamma (PPAR-γ)

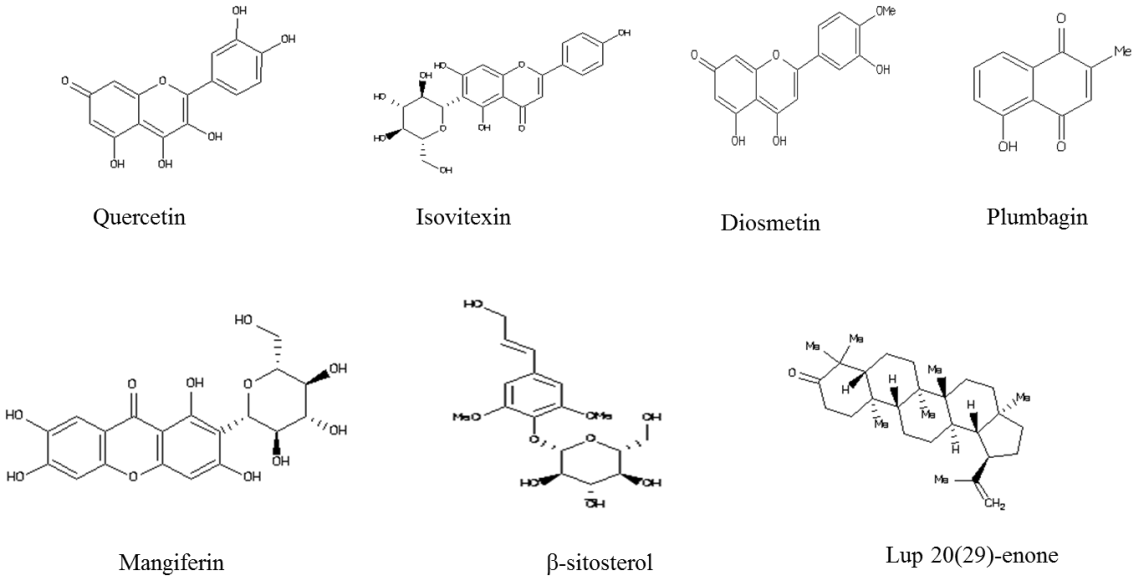

Figure 2 Structures of ligands

2. Methodology

2.1. Protein preparation

3D crystal structure of peroxisome proliferator-activated receptor gamma (PPAR-γ) was downloaded from Protein Data Bank (⟨http://www.rcsb.com) [16]. The protein for docking was prepared using the protein preparation wizard of Auto dock. The missing side chains, back chains, and residues were updated. Water molecules present in the crystal structure were removed in the protein preparation process.

2.2. Ligand preparation

The ligands were imported from www.zinc15.org. The ligands imported include, plumbagin, quercetin, isovitexin, syringin, lupe-20-ene-3-one, 7-(2-hydroxyethyl)-3-methyl-8-(1-phenylethylideneaminoamino) purine 2, 6-dione, mangiferin, diosmetin and β-sitosterol. Energy minimization was done using MMFF94 force field. Energy minimization is done to help the docking program for identifying the bioactive conformer from the local minima.

2.3. Molecular modeling

Auto Dock vina was used as molecular-docking tool in order to carry out the docking simulations. The Auto Dock vina program was used to investigate ligand binding to structurally refined PPAR-γ. The grid points in X, Y and Z axis were set at 70 × 70 × 70. The grid center was placed in the active site pocket center. The grid boxes included the entire binding site of the enzyme and provided enough space for the ligand translational and rotational walk. At first dock pdb.qt files for protein and ligands were prepared. For each ligand, a docking experiment consisting of 100 stimulations was performed and the analysis was based on binding free energies and root mean square deviation (RMSD) values, and the ligand molecules were then ranked in the order of increasing docking energies. The binding energy of each cluster is the mean binding energy of all the conformations. The clusters were ranked by the lowest-energy representative of each binding mode.

2.4. Molecular docking studies

Nine phytochemicals namely plumbagin, quercetin, isovitexin, mangiferin, syringin, lupe-20-ene-3-one, 7-(2-hydroxyethyl)-3-methyl-8-(1-phenylethylideneaminoamino) purine 2, 6-dione, diosmetin and β sitosterol and pioglitazone a standard drug were docked against PPAR-γ using AutoDock vina, results were analyzed using binding energy.

3. Results and discussion

The results in Table 1 depict the compound code, energy of contact, degree of freedom and binding affinity of the various phytochemicals.

Table 1 Molecular Docking Analysis of Phytochemicals with PPAR-γ

Sr. No.	Ligand	Compound code	Energy of contact	DOF torsional	Binding energy Kcal/mole
1	Diosmetin	5733652	238.34	5	-8.4
2	Isovitexin	4095704	420.45	10	-8.2
3	Quercetin	3869685	275.03	6	-8.5
4	Mangiferin	4098535	393.64	10	-8.4
5	Plumbagin	58187	127.13	1	-7.7
6	β-sitosterol	8681784	870.03	7	-9.1
7	Syringin	3779261	375.80	12	-6.3
8	7-(2-hydroxyethyl)-3-methyl-8-(1-phenylethylideneaminoamino) purine 2, 6-dione	5218933	493.01	5	-8.6
9	Lupe-20-ene-3-one	4081760	780.84	1	-8.6
10	Pioglitazone	968326	230.23	7	-8.3

Docking study is particularly useful as a preparatory step for identifying ligands. It provides a quicker, more affordable and highly systematic method of discovering agonists [17]. Molecular docking studies are used to predict the binding affinity of a ligand to specific target protein [18]. The phytochemicals used in this study were reported to have significant antidiabetic characteristic in various literatures but their mechanism of action is unknown [15]. Mangiferin was found to exhibit antihyperglycemic action in Streptozocin and alloxan-induced diabetic rats. Amran *et al*., 2013, Folador *et al*., [19, 20] reported that isovitexin has antihyperglycemic activity in the treatment of alloxan-induced diabetic rats. Quercetin exhibited antihyperglycemic action in STZ + NTD-induced diabetic mice [21]. Other studies attributed the activities of these phytochemicals to inhibition of alpha glucosidase [22]. The results of the study revealed that some of the compounds have lesser binding energy than the standard drug pioglitazone which is known to bind to PPAR-γ. Low binding energy score suggest high affinity for the receptor [23]. This suggests that the mechanism of action of these phytochemicals may be due to stimulation of PPAR-γ.

4. Conclusion

Based on the findings of this study these phytochemicals; Quercetin, Isovitexin, Syringin, Lupe-20-ene-3-one, 7-(2-hydroxyethyl)-3-methyl-8-(1-phenylethylideneaminoamino) purine 2, 6-dione, mangiferin, Diosmetin and β-sitosterol can serve as source of antidiabetic drugs via their mechanism of stimulation of PPAR-γ.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest

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