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In silico Studies on Plant Derived Rutin as Potent Agonist of Peroxisome Proliferator-activated Receptor Gamma (PPARγ)

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Aims: Peroxisome proliferator-activated receptor gamma (PPARγ) agonists are beneficial in the management of diabetes by increasing insulin sensitivity and inhibiting hepatic gluconeogenesis. The aim of the present study was to investigate PPAR-γ agonist property of rutin, a flavonoid found in many plant species compared to thiazolidenediones (TZDs) using *in silico* approach.
Methodology: Molecular docking of rutin on human PPAR-γ protein was determined by Vina plugin in PYMOL 1.3 and compared with thiazolidinediones, a known agonist of PPARγ.
Results: Rutin acts as a potential agonist with binding energy of - 7.8 kcal/mol compared to thiazolidinediones with binding energy of - 4.1 kcal/mol. The molecular interaction of rutin was at residues of GLU 319, ILE 369, LEU 368, MET 362, PHE 321, PHE 310, LEU 497, ALA 320, LYS 289, ILE 354.
Conclusion: We conclude that rutin is a better PPARγ agonist than TZDs confirming the capability of rutin for binding at the active site of the PPARγ.

Keywords: Diabetes; insulin sensitizer; in silico; drug development; molecular docking; bioinformatics.

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1. INTRODUCTION

The most prevalent endocrine-metabolic diseases globally are type 2 diabetes and obesity which are characterized by insulin secretion defect and insulin resistance or both leading to disturbance in carbohydrates, lipids, and protein metabolism [1-3].

Several studies have identified peroxisome proliferator-activated receptor as key regulators of glucose and lipid metabolism [4,5], because they act as transcription factors activating protein synthesis in a wide variety of processes such as energetic metabolism, proliferation, and cellular differentiation. Three isoforms of PPAR have been identified (PPAR alpha, PPAR beta/delta, PPAR gamma) [6,7]. Peroxisome proliferator-activated receptor gamma (PPARγ) has been implicated in the pathology of numerous diseases including obesity, diabetes, and atherosclerosis and cancer [2], because of its role in decreasing insulin resistance and inflammation [8-10].

PPARγ has been the focus of intense research during the past decades because agonists for this receptor have emerged as potent insulin sensitizers used in the treatment of type 2 diabetes [10,11].

The thiazolidenediones (TZDs) are agonists of PPARγ, increasing the tissues sensitivity (muscle, adiposity tissue, and liver) to insulin action [12]; hence, their use nowadays in the treatment of type 2 diabetes mellitus. Thiazolidinediones regulate the expression of several genes involved in the regulation of glucose, lipid and protein metabolism, enhancing the action of insulin in insulin-sensitive tissue by increasing glucose uptake in skeletal muscle and adipose tissue, and decreasing hepatic glucose production [7,13]. TZDs drugs produce several side effects, such as weight gain, edema, anemia, pulmonary edema, and congestive cardiac failure. Also, their use is linked to an increased in the myocardium infarction risk [14]. There is the need to search for new peroxisome proliferator-activated receptor-gamma agonist with little or no side effect. In search for new agonist with greater affinity for PPARγ, we investigated whether rutin is a good ligand of the PPARγ, the target protein that directly activate genes of the glucose-sensing apparatus in liver and pancreatic beta-cells.

2. MATERIALS AND METHODS

2.1 Protein Preparation and Generation of 3-D Structure through Homology Modeling

The starting structure (PDB ID: 4EMA) required for docking was retrieved from the protein data bank repository (http: //www.rcsb.org). Prior to docking, water and ligand coordinates were deleted. Human PPARγ "Fasta" file was downloaded from www.pubmed.org and used to model the starting structure of PPARγ used in the current study. Homology modeling was done on Swissmodel Server (http://swissmodel.expasy.org). This requires a sequence of known 3D structure with significant similarity with the target sequence. The co-ordinate file of template from protein data bank (PDB ID: 4EMA) was used to model the 3D structure of PPARγ.

2.2 Ligand Preparation for Docking

The structure of rutin and thiazolidenediones was downloaded from pubmedchem with ID: 5280805 and 5437 respectively and optimized for docking studies. The optimized ligand molecules were docked into refined PPARγ model using Vina plugin in PYMOL 1.3.

2.3 Molecular Docking

Molecular Docking calculations were performed through BSP-SLIM and VINA. The modeled structure of PPARγ molecule and rutin or thiazolidenediones was loaded on BSP-SLIM server to identify the binding pocket and pose of the ligand. BSP-SLIM is known as a blind docking method, which primary uses the structural template match to identify putative ligand binding sites, followed by fine-tuning and ranking of ligand conformations in the binding sites through the SLIM-based shape and chemical feature comparisons [15]. All the water molecules were removed prior to docking and Vina algorithm was used for the docking procedure.

2.4 Data Analysis

Protein snapshots were taken using PYMOL.

3. RESULTS AND DISCUSSION

Protein-ligand docking is a key computational method in the design and starting points for the drug discovery process. The detection of ligand-binding sites is often the starting point for protein function identification and drug discovery [16]. In the current study, to understand the interactions between the ligands and PPARγ protein and to explore their binding mode, docking study was performed using BSP-SLIM and Vina plugin in PYMOL 1.3.

The crystal structure of the PPARγ using (4EMA) as template was modeled and used as a target for docking simulation. The structure of rutin (Fig. 1a) and thiazolidenediones (Fig. 1b) were downloaded from pubmedchem and prepared for the docking (3D) using Chemaxon. The Fasta sequence of PPARγ was obtained from pubmed and used to model the 3D structure of PPARγ on swissmodel server (Fig. 2). In the current study, we have taken the receptor human PPARγ and identified rutin as a ligand of this receptor. When PPARγ was docked with thiazolidinediones (TZDs), a known drug (PPARγ agonist), the energy value of (-4.1 kcal/mol) (Fig. 3) was obtained. When rutin was docked against the same receptor (PPARγ), a binding energy of -7.8 kcal/mol (Fig. 4) was obtained making it a better ligand for PPARγ than TZDs. Both TZDs and rutin interacted at the same binding pocket within the PPARγ molecule (Fig. 6).

The present study helps us to understand the interaction between the ligand, rutin and receptor PPARγ protein and also explore their binding mode. Both TZDs and rutin were docked at the active site of PPARγ. The amino acid residues in the active site are the main contributors to the PPARγ-ligand interactions. The amino acid residues within 4A that stabilized the TZDs-PPARγ interaction are CYS 313, TYR 355, HIS 351, HIS 477, SER 317, TYR 501, LEU 497, (Fig. 7) while those that stabilized rutin-PPARγ interaction are GLU 319, ILE 369, LEU 368, MET 362, PHE 321, PHE 310, LEU 497, ALA 320, LYS 289, ILE 354 (Fig. 8).

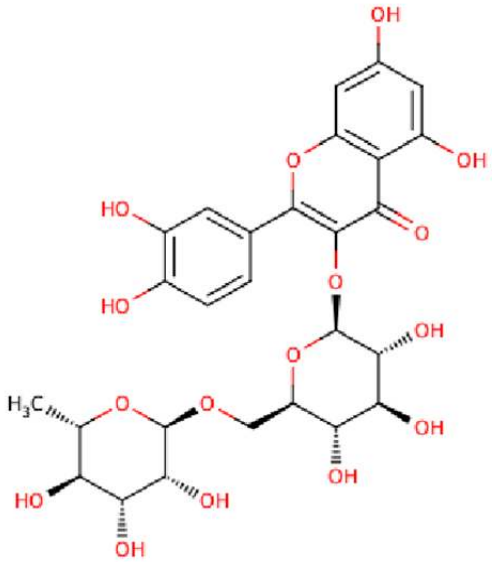

Fig. 1a. 2D structure of rutin

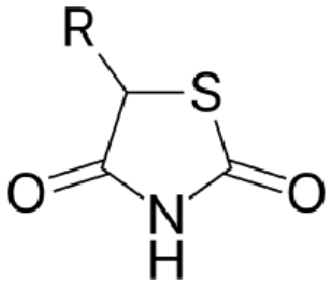

Fig. 1b. 2D structure of thiazolidinedione (TZDs)

Table 1. Showing binding energy in Kcal/mol of thiazolidinediones (TZDs) with PPARγ

Mode	Affinity (Kcal/mol)	Distance from rmsd l.b.	Best mode rsmd u.b.
1	-4.1	0.000	0.000
2	-4.1	0.881	2.939
3	-4.0	2.309	2.599
4	-4.0	2.301	3.047
5	-3.9	1.514	3.150
6	-3.8	1.933	2.579
7	-3.8	2.205	3.454
8	-3.8	2.123	2.379
9	-3.7	2.592	2.904
10	-3.7	2.686	2.985

Table 2. Showing binding energy in Kcal/mol of rutin with PPARγ

Mode	Affinity (Kcal/mol)	Distance from rmsd l.b.	Best mode rsmd u.b.
1	-7.8	0.000	0.000
2	-7.8	2.742	9.185
3	-7.7	2.666	7.913
4	-7.1	1.756	5.315
5	-6.8	3.184	9.070
6	-6.8	4.117	9.622
7	-6.7	2.115	5.990
8	-6.6	3.866	8.201
9	-6.6	1.899	8.579
10	-6.4	3.124	8.673

MTMVDTEMPFWPTNFGISSVDLSVMEDHSHSFDIKPFTTVDFSSISTPHYEDIPFTRTDPVVADYKYDLK
LQEYQSAIKVEPASPPYYSEKTQLYNKPHEEPSNSLMAIECRVCGDKASGFHYGVHACEGCKGFFRRTIR
LKLIYDRCDLNCRIHKKSRNKCQYCRFQKCLAVGMSHNAIRFGRMPQAEKEKLLAEISSDIDQLNPESAD
LRALAKHLYDSYIKSFPLTKAKARAILTGKTTDKSPFVIYDMNSLMMGEDKIKFKHITPLQEQSKEVAIR
IFQGCQFRSVEAVQEITEYAKSIPGFVNLDLNDQVTLLKYGVHEIIYTMLASLMNKDGVLISEGQGFMTR
EFLKSLRKPFGDFMEPKFEFAVKFNALELDDSDLAIFIAVIILSGDRPGLLNVKPIEDIQDNLLQALELQ
LKLNHPESSQLFAKLLQKMTDLRQIVTEHVQLLQVIKKTETDMSLHPLLQEIYKDLY

Fig. 2. Amino acid sequence of PPARγ

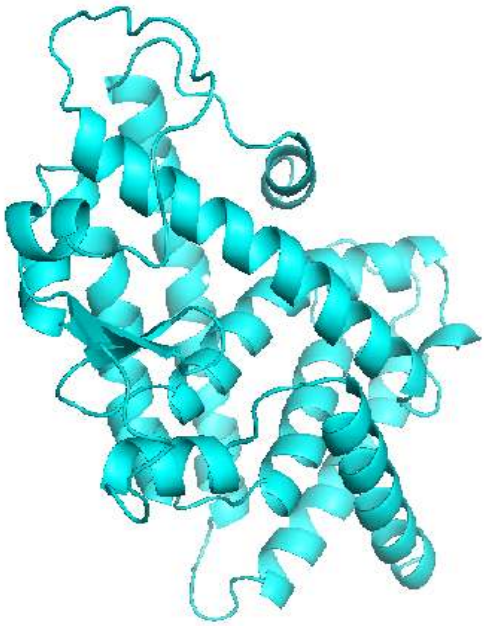

Fig. 3. 3D structure of human peroxisome proliferator-activated receptor gamma (PPARγ)

The ability of rutin to have better interaction with PPARγ could be due to the amino acid residues found within 4A distance within the binding pocket that are not found in TZDs-PPARγ interaction. These amino acids could be instrumental to the better interaction and the higher affinity of PPARγ to rutin than TZDs. From this study, we conclude that rutin is a better

PPARγ agonist than TZDs but further animal and human studies are needed to corroborate this and compare the level of safety of rutin with Thiazolidenediones.

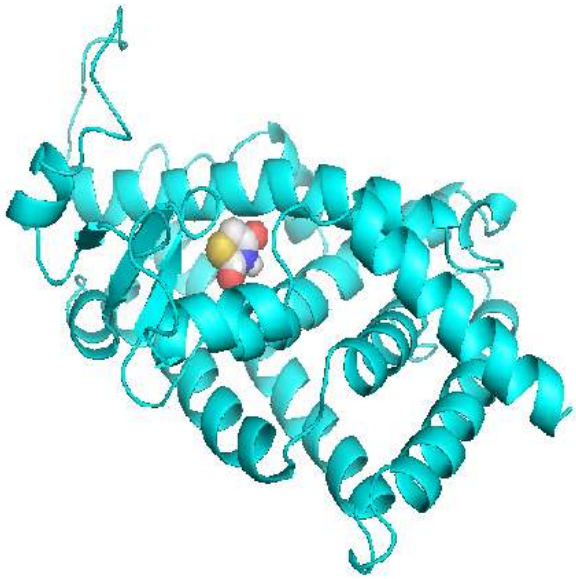

Fig. 4. Binding pose/mode of PPARγ with thiazolidinediones (PPARγ agonist) with -4.1 kcal/mol binding affinity

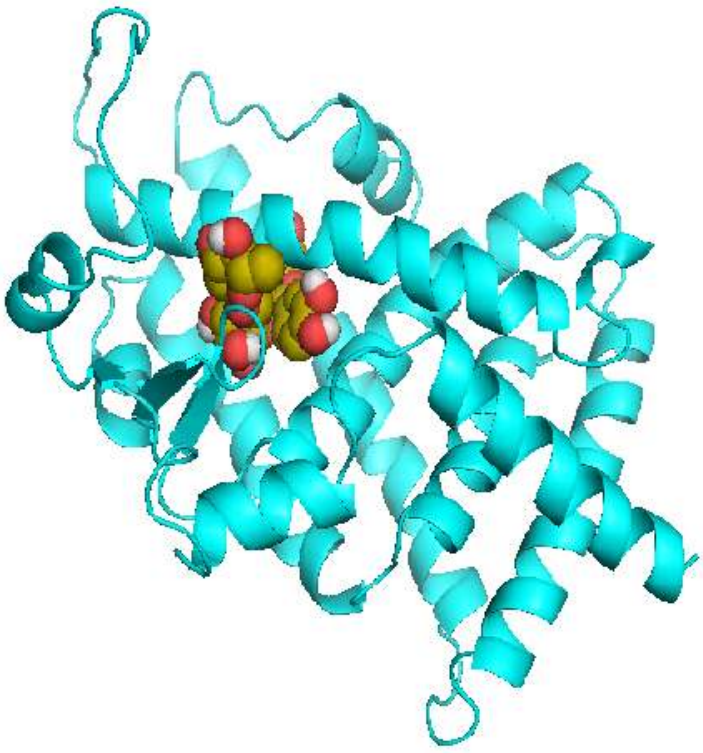

Fig. 5. Binding pose/mode of PPARγ with rutin with -7.8 kcal/mol binding affinity

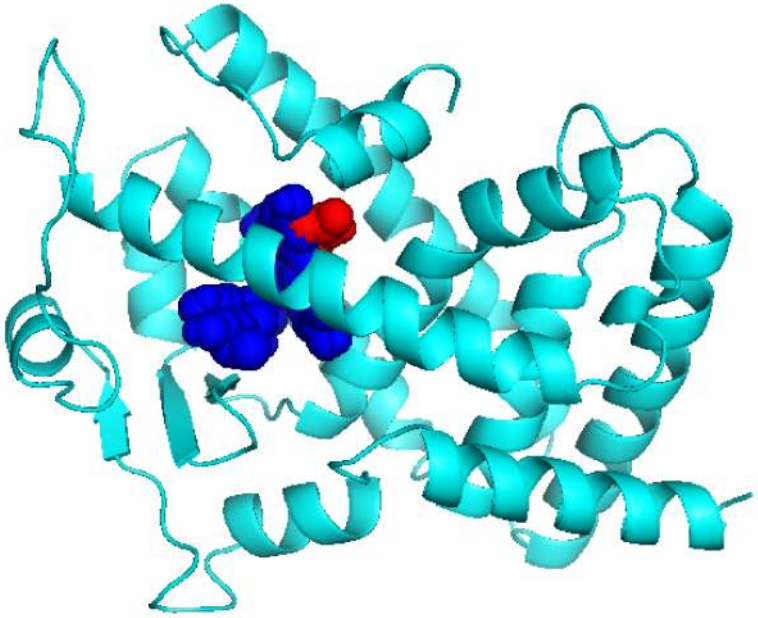

Fig. 6. Binding pose of PPARγ with rutin (blue) plus known agonist drug thiazolidinediones (red)

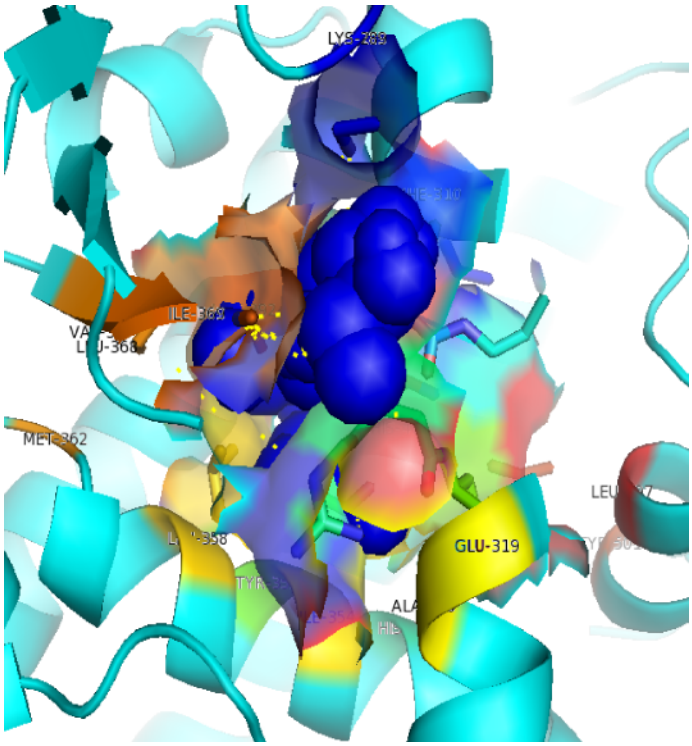

Fig. 7. Binding pose of PPARγ with rutin showing amino acid residue within 4 Armstrong of ligand binding site

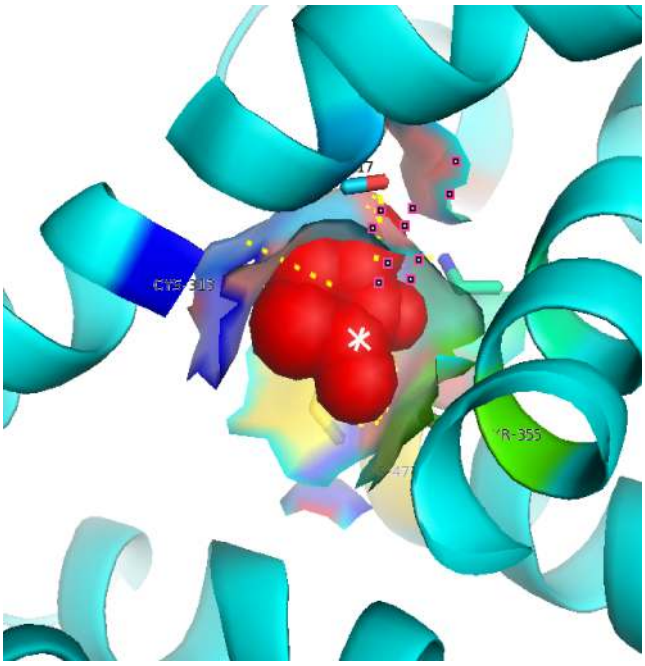

Fig. 8. Binding pose of PPARγ with thiazolidinediones (TZDs) showing amino acid residue within 4 Armstrong of ligand binding site

4. CONCLUSION

The molecular docking studies with TZDs and rutin into the binding cavity of PPARγ showed that rutin have more favourable interaction than PPARγ with better docking score. The results of our present study can be useful for the design and development of novel compounds having better PPARγ agonist activity which can consequently be use to cure/manage type 2 diabetes mellitus.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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