A molecular docking approach of some drugs on mutant PPARγ against Type-II Diabetes

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Absract **- Type-II Diabetes is now proved itself as a strong problem for human beings. Among various proteins of type-II Diabetes, PPARγ plays very important role as it is the only receptor of Thiazolidinediones (TZDs) types of drugs. But in some journals it has been found that due to some mutation, it fails to bind these drugs at their drug binding site. Here the mutation is introduced to the wild type protein and stability was checked by energy minimization. By docking study it was suggested that when Thiazolidinediones (TZDs) types of drugs can not bind, then some drugs which can bind with a high efficiency even after mutation.**

Index Terms **-Type-II Diabetes, Thiazolidinediones (TZDs), Docking, Binding energy, interacting residues**

I. INTRODUCTION

Now-a-days many more dreadful diseases are showing their bad effects to human society. Among them Diabetes is also playing very important role. There are two types of Diabetes like type-I and type-II. Type-I is caused due to lack of insulin secretion inside body in case of type-II diabetes, the body can capable to secret insulin but the cell does not respond it. In other way, cell increases its resistant capacity towards insulin [1]. Peroxisome proliferator-activated receptor gamma (PPAR-γ or PPARG) is a protein which is the only receptor of Thiazolidinediones (TZDs) types of drugs [2] like Actos (Generic name=Rosiglitazone, Rating= 6.0), Avandia (Generic name=Pioglitazone, Rating= 5.3)and Rezulin (Generic name= Troglitazone, Rating= 0.0) [3]. It is also called Glitazone receptor, NR1C3, PPARG1, PPARG2. It is a nuclear receptor of sub family 1, group C, member 3 having location in nucleus, cytoplasm, and chromosome 3p 25.2. Mostly its tissue specificity is in adipose tissue, few in skeletal muscle, spleen, hert, liver, lung, placenta, ovary etc [4]. The literature study supports that these drugs bind at its drug binding site of PPARγ. Sothat the resistivity of the cell decreases and insulin sensitivity increases. It also results reduction of blood glucose. But due to some mutation like P467L and V290M at the drug binding site, the Thiazolidinediones (TZDs) fails to bind properly and the original function of the drugs decrease.

II. MATERIALS AND METHODS

The tertiary structure was downloaded from PDB (4EM9) as it has better resolution. The two mutations P467L, V290M were put by using PyMol. Energy minimization was done with ModRefiner[9] in order to make the predicted tertiary mutant structure more stable. To check the Root Mean Square (RMS) value, the mutant protein was superposed/ aligned on the energy minimized structure of mutant protein. The specific drug binding site was selected from the literature study [5][6]. So that the 3D structure of Thiazolidinediones (TZDs) type of drugs and other available drugs for type-II Diabetes were collected from PubChem[8] and was docked with that site with the help of AutoDock-4.2 algorithm [7]. During protein file setup the kollman charge and Hydrogen was added to the macromolecule and the number of run was set as 100. It was set by keeping the two mutated residues (P467L and V290M) flexible. The docking results were analyzed.

III. RESULT AND DISCUSSION

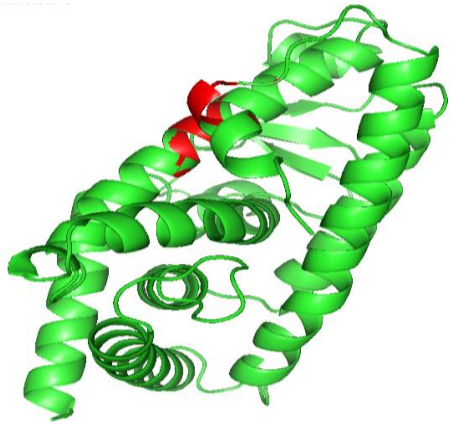

Fig. 1: Alignment of mutant PPARγ with energy minimized mutant PPARγ

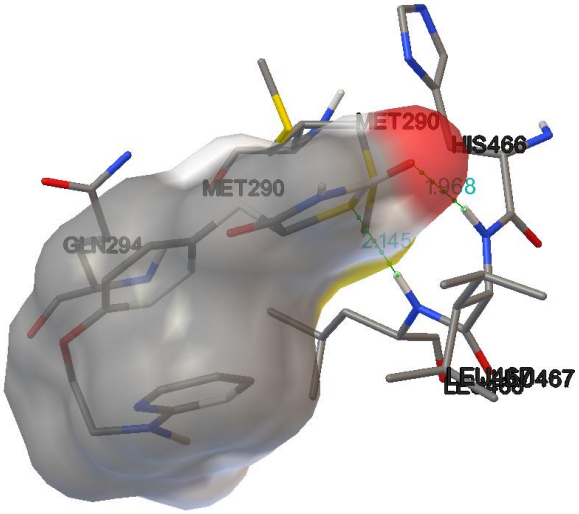

Fig.2 (b): Interaction between protein- Avandia

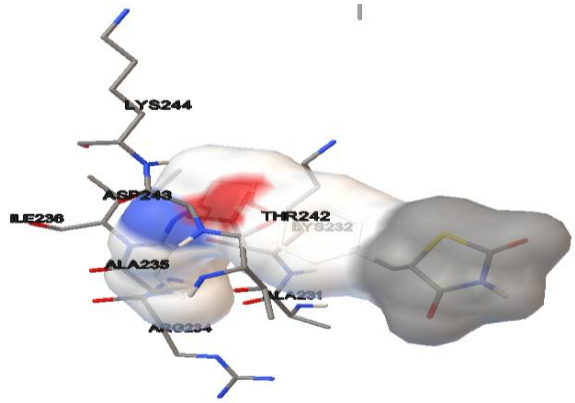

Fig. 2(a): Interaction between protein-Actos.

Sl no.	Drugs name	Docked energy	KI value	Torsion energy	Interacting residues and H bond	H bond length	H bond energy
1	Actos	-2.49	21.07mM	2.09	ILE236 ASP243 ALA235 LYS244 ARG234 ALA231 LYS232 THR242		
2	Avandia	-3.03	6.06mM	2.09	LEU468(O…H) LEU467(O…H) HIS466 MET290 GLN294	2.145 1.968	-6.771 -5.216
3	Rezulin	-2.3	24.35mM	1.79	MET290 LEU467(O…H) LEU468 GLU471(H…O)	1.999 2.039	-4.112 -0.373

Table1: Autodock analysis of Thiazolidinediones (TZDs) type of drugs.

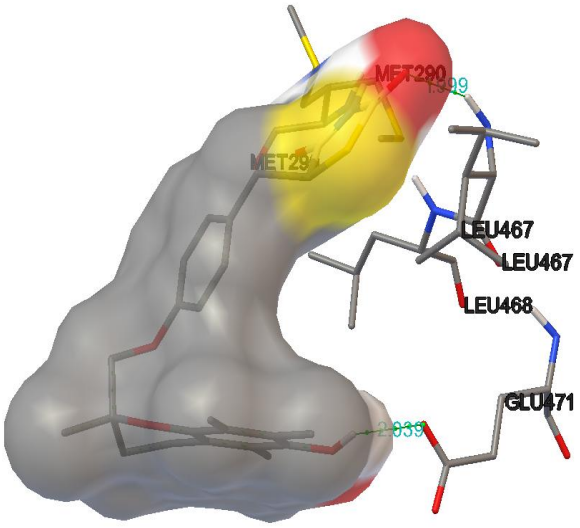

Fig. 2(c): Interaction between protein-Rezulin

The reported mutations were at the binding region of the PPARγ. So that the structure was mutated and energy minimized and then alignment was performed to test the root mean square value by using PyMol. It was found as 0.01 and identified that the structure has the better stability. The further flexible docking result analysis was shown that all the Thiazolidinediones (TZDs) type of drugs bind with a very less affinity as these were having very less docked energy and KI value. The energy at H-bond were also very poor (Table1). So over all it was found as supported data as literatures

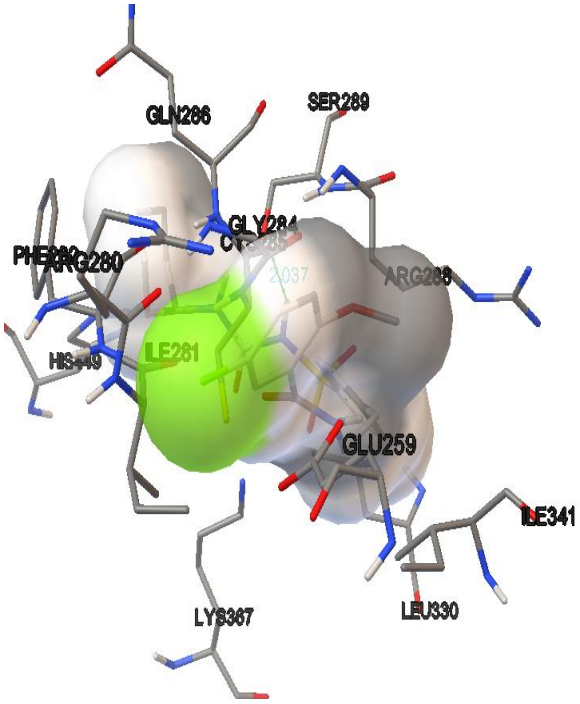

Fig 3(a): Interaction between protein- Glibenclamide

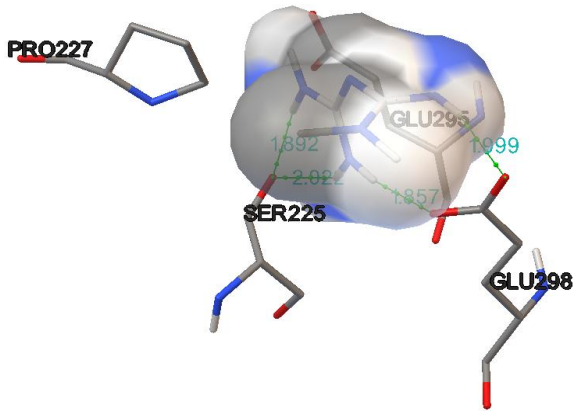

Fig 3(b): Interaction between protein- metformin

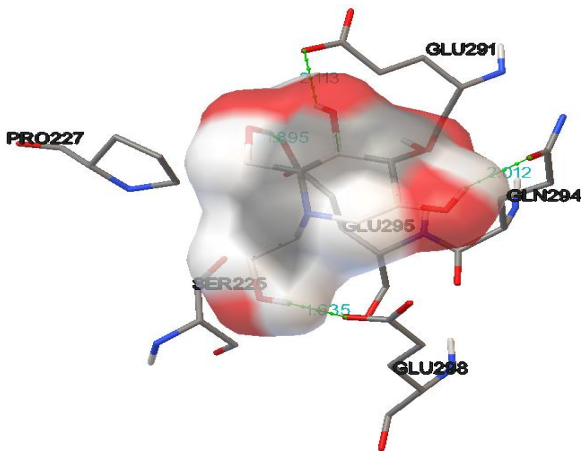

Fig 3(c): Interaction between protein- Miglitol

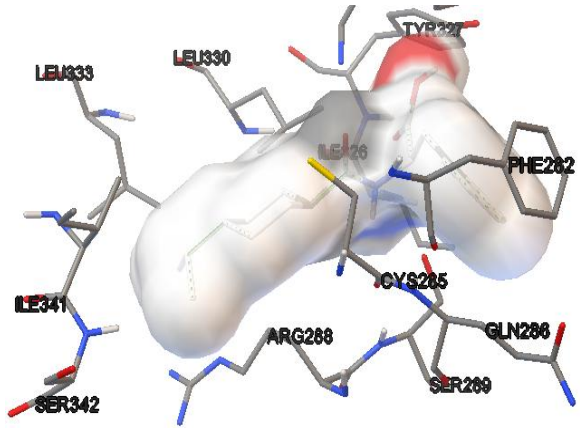

Fig 3(d): Interaction between protein- Nateglinide

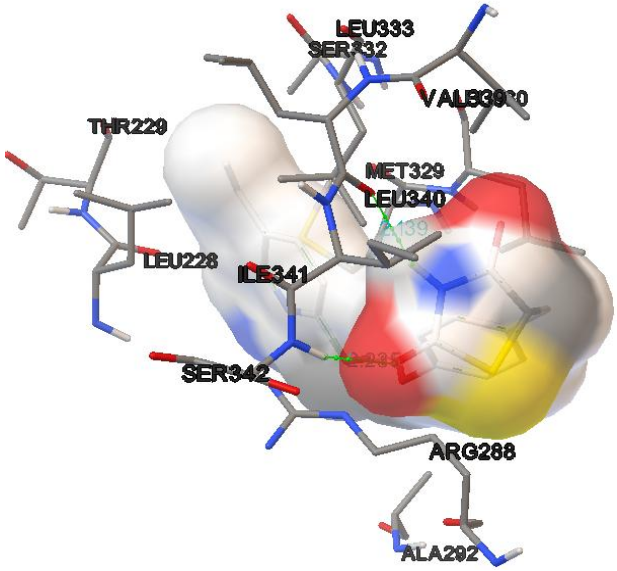

Fig 3(e): Interaction between protein- Pioglitazone

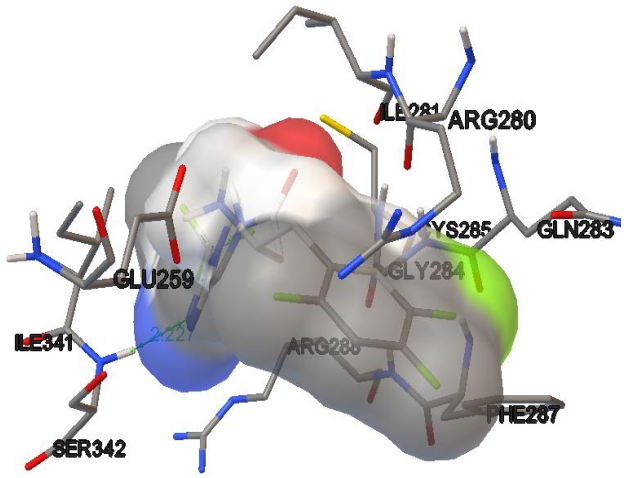

Fig 3(f): Interaction between protein-Sitagliptin

Table2: Autodock analysis of other available drugs

Sl no.	Drugs name	Docked energy	KI value	Torsion energy
1	Glibenclamide	-10.75	13.14nm	2.39
2	Metformin	-5.63	74.29um	0.0
3	Miglitol	-4.64	396.84um	2.39
4	Nateglinide	-8.61	486.3nm	2.09
5	Pioglitazone	-7.79	1.95um	2.09
6	Sitagliptin	-8.29	844.66nm	1.79

Again the molecular docking was performed among the protein and other available drugs to find out the interaction. It was found that the docked energy and the KI value were better than in case of Thiazolidinediones (TZDs) type of drugs. In some cases like Glibenclamide, Nateglimide, Sitagliptin and Pioglitazone the docked energy and KI values were very high. Metformin, Miglitol and Pioglitazone show many H-bond interaction with a better bond energy. So over all it was identified that these all six drugs have the ability to bind at the drug binding site of PPAR gamma protein even after mutation.

IV. CONCLUSION

The study indicates that PPAR gamma is a suitable target for type-II Diabetes as it has the capacity to bind drugs at specific drug binding site and can increases insulin sensitivity of the cell. Due to the mutations at drug binding site, the Thiazolidinediones (TZDs) type of drugs fails to interact properly as it has the less binding affinity towards the protein. On the other hand, the docked energy, KI value, interacting residues, H- bond length and energy gives a prediction for creation of better drug[Table-2]. So during this condition, we may put such above drugs which can bind with a high affinity and can accelerate the function of protein towards insulin sensitivity and ultimately create a novel step towards win over Diabetes.

Table 2: H-Bond analysis of Interacting residue

Interacting residues	H–bond residue	Bomd length	Bond Energy
LEU330, LYS367, ILE341, GLU259, ILE281, HIS449, PHE262, ARG280, ARG288, GLY284, CYS285, GLN286, SER289	**CYS285(H…O)**	**2.037**	**-3.318**
PRO227, SER225, GLU298, GLU295	**PRO227(H…O)** **SER225(H…O)** **GLU298(H...O)** **GLU295(H...O)**	**1.892** **2.022** **1.999** **1.857**	**-2.7** **-2.004** **-0.15** **,-6.468**
GLU291, PRO227, GLN294, GLU295, SER225, GLU298	**GLU291(H…O)** **GLN294(H…O)** **GLU295(H…O)** **GLU298(H…O)**	**2.113** **2.012** **1.895** **1.635**	**-0.069** **-0.997** **-3.495** **-1.042**
SER342, LEU333, LEU330, TYR327, ILE226, PHE282, CYS285, ARG288, ILE341, GLN288, SER289			
LEU333, SER332, VAL339, MET329, THR229, LEU228, ILE341, SER342, SER342, ARG288, ALA292, LEU340	**SER342(O..H)** **LEU340(H..O)**	**2.235** **2.139**	**-3.692** **-3.247**
ILE281, ARG280, CYS285, SER342, GLN283, GLY284, ARG288, PHE287, GLU259, ILE341	**SER342(O...H)**	**2.227**	**-3.681**

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