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DOCKING STUDY OF CHLOROGENIC ACID ON PPAR – γ FOR SCREENING OF ANTIOBESITY ACTIVITY

Kumar Pratyush* and Alpana Asnani

Priyadarshini J.L. College of Pharmacy, Electronic Building, Electronic Zone, M.I.D.C, Hingna Road, Nagpur.

***Corresponding Author: Kumar Pratyush**
Priyadarshini J.L. College of Pharmacy, Electronic Building, Electronic Zone, M.I.D.C, Hingna Road, Nagpur.

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ABSTRACT
Objective: Screening of chlorogenic acid for anti obesity action by molecular docking on PPAR – γ receptor. The different conformations were critically studied. **Methods:** Molecular docking studies were carried out by the help of software *AUTODOCK*. Conformations were studied using *PyMol* software. **Results:** Conformations were studied and the numbers of hydrogen bonds formed were analyzed and tabulated. **Conclusion:** Best 10 conformations were selected by *AUTODOCK* software that showed that 9 such conformations formed hydrogen bonds. Formation of these hydrogen bonds justifies that chlorogenic acid shows better binding towards PPAR-γ receptor which shows anti obesity activity.

KEYWORDS: Chlorogenic acid, PPAR-γ, Anti obesity, Autodock, Pymol.

INTRODUCTION
Peroxisomes are subcellular organelles found in most plant and animal cells that perform diverse metabolic functions including H_2O_2-based respiration, β-oxidation of fatty acids (FAs), and cholesterol metabolism. Peroxisome proliferator- activated receptors (PPARs) proteins belong to superfamily of phylogenetically related protein termed nuclear hormone factor.[1] PPARs were identified in rodents in 1990 and these belong to a nuclear hormone receptor superfamily containing 48 members. But, these agents are associated with no proliferation in the human beings. Structurally, PPARs are similar to steroid or thyroid hormone receptor and are stimulated in response to small lipophilic ligands. In rodents, a large class of structurally related chemicals including herbicides, industrial solvents, and hypolipidemic drugs lead to significant increase in the number and size of peroxisomes in the liver and may cause liver hypertrophy, liver hyperplasia, hepatocarcinogenesis, and transcription of genes encoding proximal enzymes. PPARs mainly exist in three subtypes; α, β/δ, and γ, each of which mediates the physiological actions of a large variety of FAs and FA-derived molecules. Activated PPARs are also capable of transcriptional repression through DNA-independent protein-protein interactions with other transcription factors such as NFκB signal activators and transducers of transcription STAT-1 and AP-1 signaling.[2]

Isoforms of peroxisome proliferator- activated receptors
PPARs are transcription factors that belong to the Superfamily of nuclear receptors. Other members of this family include retinoic acid, estrogen, thyroid, vitamin D and glucocorticoid receptors and several other proteins involved in xenobiotic metabolism PPARs act on DNA response elements as heterodimers with the retinoid X receptor (RXR). Their natural activating ligands are lipid- derived substrates. The family of PPARs is represented by the following three members: PPAR-α, PPAR-δ and PPAR-γ. They play an essential role in energy metabolism; however, they differ in the spectrum of their activity— PPAR-γ regulates energy storage, whereas PPAR-α is expressed predominantly in the liver, and to a lesser extent, in muscle, in the heart and in bone and PPAR-δ present ubiquitously expressed in whole body regulate energy expenditure; expression of PPAR-γ in endothelial cells, vascular smooth muscle cells. PPAR-γ is further subdivided in four isoforms.[3]

- γ1 - expressed in virtually all tissues, including heart, muscle, colon, kidney, pancreas, and spleen.
- γ2 - expressed mainly in adipose tissue (30 amino acids longer).
- γ3 - expressed in macrophages, large intestine, and white adipose tissue.
- γ4 - expressed in endothelial cells.

Mechanism of action of PPAR-γ
Thiazolidinediones (TZDs) are the most widely studied PPAR-γ ligands. Troglitazone was the first drug approved for this use, followed by rosiglitazone and pioglitazone. The mechanism of action of TZDs was

not known until 1995, when Lehmann reported that TZDs were high affinity ligands, for Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a ligand-dependent transcription factor and a member of the nuclear receptor superfamily. Acting as sensors of hormones, vitamins, endogenous metabolites and xenobiotic compounds, the nuclear receptors control the expression of a very large number of genes. PPAR-γ has been known for some time to regulate adipocyte differentiation, FA storage and glucose metabolism and is a target of antidiabetic drugs.[4] PPAR-γ agonist improves insulin resistance by opposing the effect of TNF-α in adipocytes.[5] Various modulator of PPAR-γ agonist is shown in Balakumar P. 2007.[6] PPAR-γ enhances the expression of a number of genes encoding proteins involved in glucose and lipid metabolism.[7]

Green Tea

Green tea is a major supplement in diet of today's population. It adds greater immunity, antioxidant property and many more pharmacological effects. It also acts as anti obesity agent which is used to decrease obesity. Chlorogenic acid is one of the major component of green tea. It has better binding towards the PPAR- γ receptor.

MATERIAL AND METHODS

Chemical structure of chlorogenic acid was made by the help of *ChemSketch* software and the structure was cleaned. Molecular docking studies were carried out *AUTODOCK 4.0*[8] software in lab of Priyadarshini J.L. College of Pharmacy, Nagpur.

METHODOLOGY

1. Selection of X-ray crystal structure of the target proteins (PPAR-PDB) & minimizing the energy of the entire model.
2. Downloading the crystal structure of proteins in. *pdb format* (3R8A).
3. Identifying the active site of the protein.
4. Ligand building & energy minimization.
5. Docking Ligands into the active site of the protein.

RESULTS AND DISCUSSION

The results of the docking studies are shown in Table 1 and the binding interactions of different conformations are shown in figure 1-10.

Table 1

S. No.	Conformations	Binding Energy	No. of Hydrogen Bonds
1	Conformation 1	- 7.71	3
2	Conformation 2	- 6.31	0
3	Conformation 3	-7.39	1
4	Conformation 4	-6.98	3
5	Conformation 5	-7.66	2
6	Conformation 6	-6.95	1
7	Conformation 7	-7.88	1
8	Conformation 8	-7.81	2
9	Conformation 9	-7.92	1
10	Conformation 10	-6.82	2

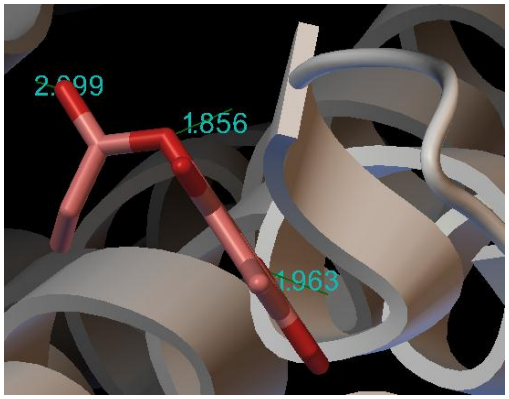


Figure 1

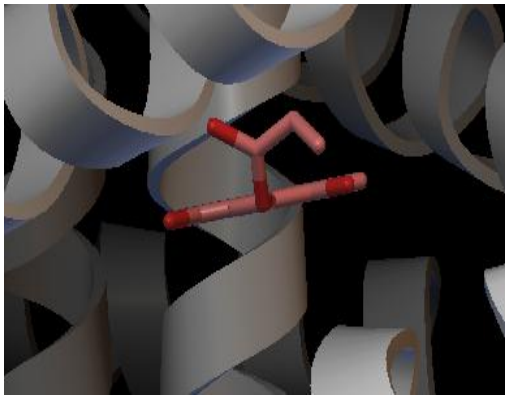


Figure 2

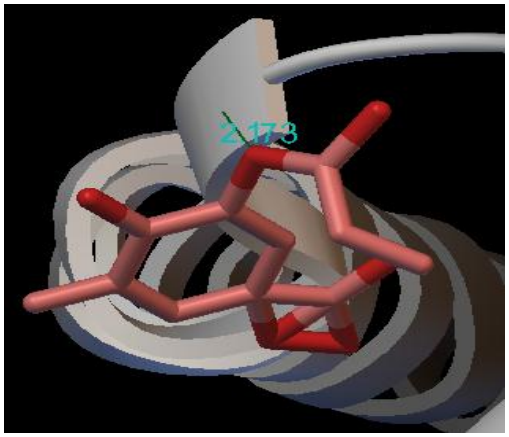


Figure 3

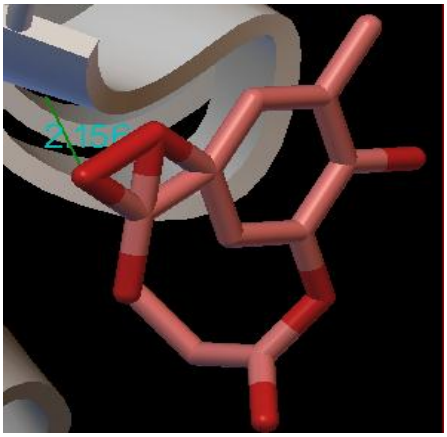


Figure 7

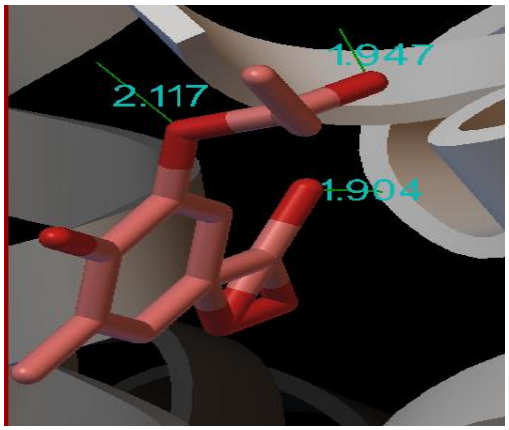


Figure 4

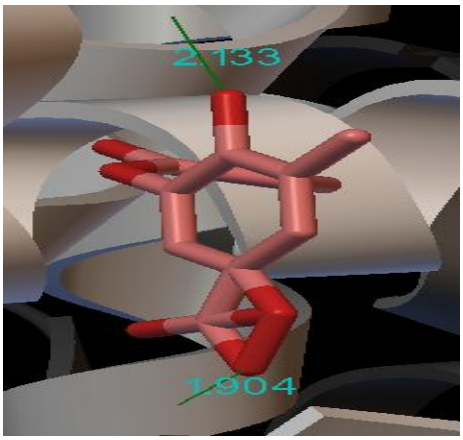


Figure 8

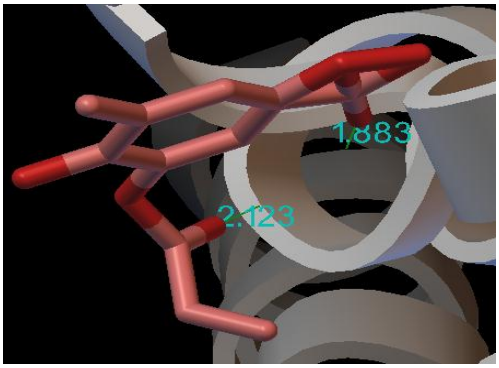
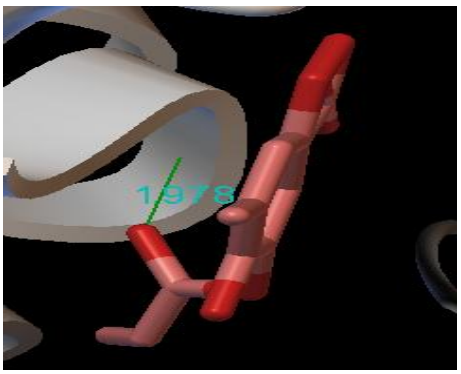


Figure 5



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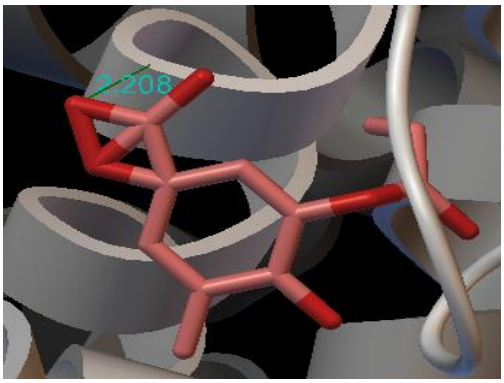

Figure 6

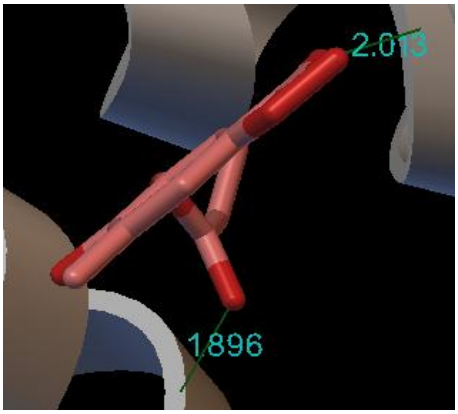

Figure 10

CONCLUSION

The results of docking studies show better binding to the PPAR-γ receptor. Study of best conformations reveals that 9 out of best 10 conformations exhibit hydrogen bond formation. So we can suggest that chlorogenic acid present in the green tea is the active agent that leads to decrease obesity.

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