Life Science Informatics Publications
Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences
Journal Home page http://www.rjlbpcs.com/
RJLBPCS
ISSN 2454-6348

Original Research Article **DOI - 10.26479/2017.0301.04**

INSILICO IDENTIFICATION OF POTENT PPAR AGONISTS FROM *RHEUM EMODI* PLANT COMPOUNDS

Radhika Ravindran*, Sudarsanam Dorairaj

Department of Advanced Zoology and Biotechnology, School of Genome, Loyola College, Chennai.

ABSTRACT: PPARs are members of the nuclear hormone receptor super family that bind to specific DNA response elements as heterodimers with the retinoid X receptor. The endogenous activators of all members of the PPAR family are a variety of fatty acids, which suggests that the PPARs are highly involved in lipid metabolism. The role of PPAR in combating diabetes has provided us the rationale to carry out structure based drug design studies. Docking results of PPAR γ with emodin, chrysophanol and the drug glibenclamide are performed using Glide. The finding suggests that both the components of *R.emodi* could serve as PPAR-γ agonists.

KEYWORDS: PPAR, Type 2 diabetes, Docking, Chrysophanol, emodin, agonists

***Corresponding Author: Dr. Radhika Ravindran** Ph.D.

Department of Advanced Zoology and Biotechnology, School of Genome, Loyola College, Chennai

* Email Address: radikaravindran@gmail.com

1. INTRODUCTION

PPARs are members of the nuclear hormone receptor super family that bind to specific DNA response elements as heterodimers with the retinoid X receptor (Robert *et al.,* 2006). The peroxisome proliferator-activated receptors (PPARs) are involved in the regulation of lipid and glucose metabolism (Willson *et al*., 2001). They are ligand-dependent transcription factors that contain an N-terminal activation domain, DNA-binding domain, and ligand-binding domain (Renaud and Moras, 2000). PPARs activate target genes by binding to response elements located within regulatory regions of these target genes (Laudet and Gronemeyer, 2002). Three subclasses of PPARs are known, called

Peer review under responsibility of Life Science Informatics Publications

α, δ and γ that are coded by different genes, exhibit tissue-specific expression patterns, and are associated with various functions. Of these, PPARϒ is expressed mostly in adipose tissue, where it is essential in adipocyte differentiation and controls the storage of fatty acids, increasing triglyceride synthesis and storage within adipocytes. Activation of PPARϒ improves insulin resistance and therefore PPARϒ is an established molecular target for the treatment of type 2 diabetes (Staels and Fruchart, 2005). The role of PPAR in combating diabetes has provided us the rationale to carry out structure based drug design studies (Ostberg *et al.,* 2004). The Peroxisome Proliferator-Activated Receptor γ (PPAR-γ) has been the focus of intense research during the past decade because ligands for this receptor have emerged as potent insulin sensitizers used in the treatment of type 2 diabetes.

2. MATERIALS AND METHODS

Protein Data Bank

The Protein Data Bank (PDB) is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. The data typically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists from around the world, are freely accessible on the Internet via the websites of its member organizations PDBJ and RCSB. Most major scientific journals, and some funding agencies, such as the NIH in the USA, now require scientists to submit their structure data to the PDB (URL: http://www.rcsb.org/pdb/home/home.do).

PFAM (Protein family)

Pfam is a semi-automatic protein family database, which aims to be comprehensive as well as accurate. Unlike standard pair wise alignment methods (e.g. BLAST, FASTA). Pfam deals with multiple domain proteins (Bateman *et al*., 2004). The latest version of Pfam contains 6190 Pfam families. Pfam families match 75% of protein sequences in Swiss-Prot and TrEMBL (and 53% of all residues). The combination of Pfam A and Pfam-B covers 82% of protein sequences in Swiss-Prot and TrEMBL (URL: http://pfam.sanger.ac.uk/).

GLIDE

Glide offers the full spectrum of speed and accuracy from high-throughput virtual screening of millions of compounds to extremely accurate binding mode predictions, providing consistently high enrichment at every level. Glide exhibits excellent docking accuracy and high enrichment across a diverse range of receptor types. Software used for docking is Glide Schrodimger Suite 2012.

3. RESULTS AND DISCUSSION

The three dimensional structure of PPAR-γ (PDB ID: 3DZY) has been downloaded from PDB Database. The PPAR-γ N terminal belongs to PPAR gamma_N identified from pfam results. The 3D structures of PPAR-γ are docked with natural and synthetic compounds using Glide software. Docking results of PPAR γ with emodin, chrysophanol and the drug glibenclamide are performed using Glide. Totally two hydrogen bonds are formed between PPAR-γ and emodin. The glide score of the complex is calculated as - 4.23. Five hydrogen bond interaction are formed between PPAR-γ with chrysophanol, the glide score is noted as - 3.91(Table 1, 2). Glibenclamide formed no interaction with the target PPAR γ (Fig.1 and 2). The finding suggests that both the components of *R.emodi* could serve as PPAR-γ agonists. These findings are significant not only for the elucidation of herbal anti-diabetic mechanism but also for the development of novel PPARs agonists in diabetes therapy. In recent years, it has been reported that the effects of herbs on peroxisomal proliferator activated receptors (PPARs) are associated with the regulation of glucose and lipid metabolism. Extracts from *Astragalus membranaceous* and *Pueraria thomsonii* significantly activate PPARα and PPARγ. Several isoprenols from herbs have the dual actions on both PPARα and PPARγ in vitro (Shen *et al*., 2006). Emodin from *R. Palmatum* is a potent PPARγ agonists could render it as an attractive therapeutic agent for managing diabetes mellitus (Jianfeng *et al*., 2010). A novel class of PPAR dual agonists is discovered based on the compound GW409544, a well-known dual agonist for both PPARα and PPAR-γ (Ying *et al.,* 2012).

Table 1: Peroxisome Proliferator-Activated Receptor γ Interaction with Emodin and Chrysophanol

Protein complex	Amino acid	Protein atom	ligand atom	Bond length	Terminii	No of hydrogen bonds	G score
PPARϒ and Emodin	ARG 302	H	O	2.307	Carboxy	2	-4.23
	MET 454	O	H	1.867	Carboxy		
PPAR ϒ Chrysophanol	TYR 397	O	H	2.173	Carboxy	5	-3.91
	ARG 426	H	O	2.416	Amino		
	ARG 426	H	O	2.229	Amino		
	ARG 426	H	O	2.466	Amino		
	ARG 426	H	O	2.331	Amino		

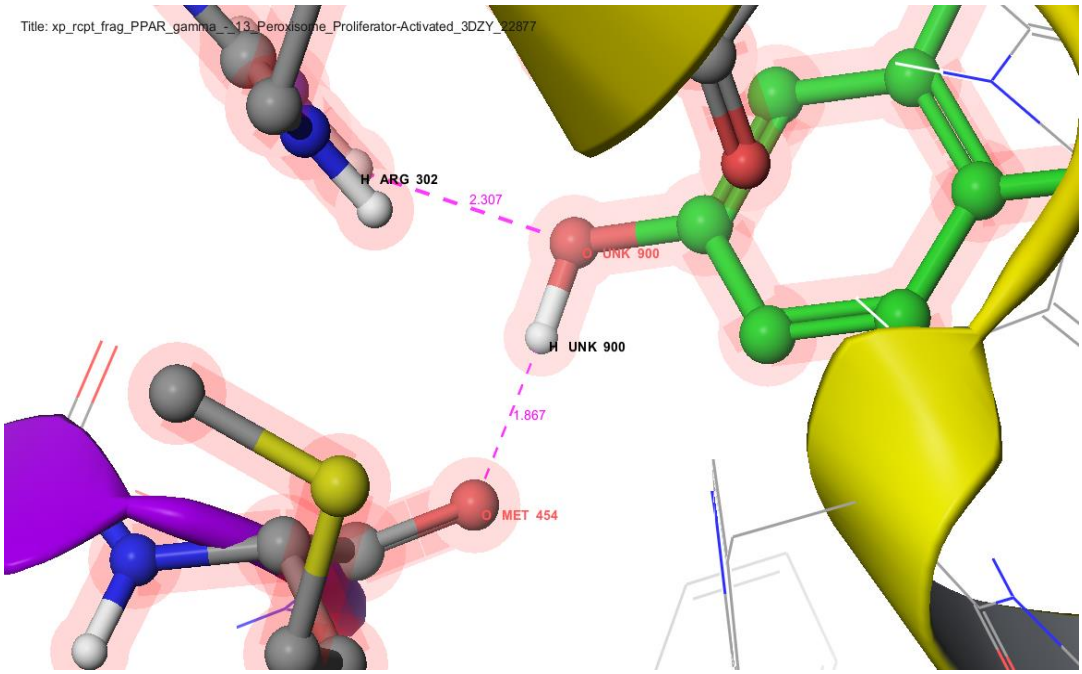

Figure 1: PPAR gamma with Emodin

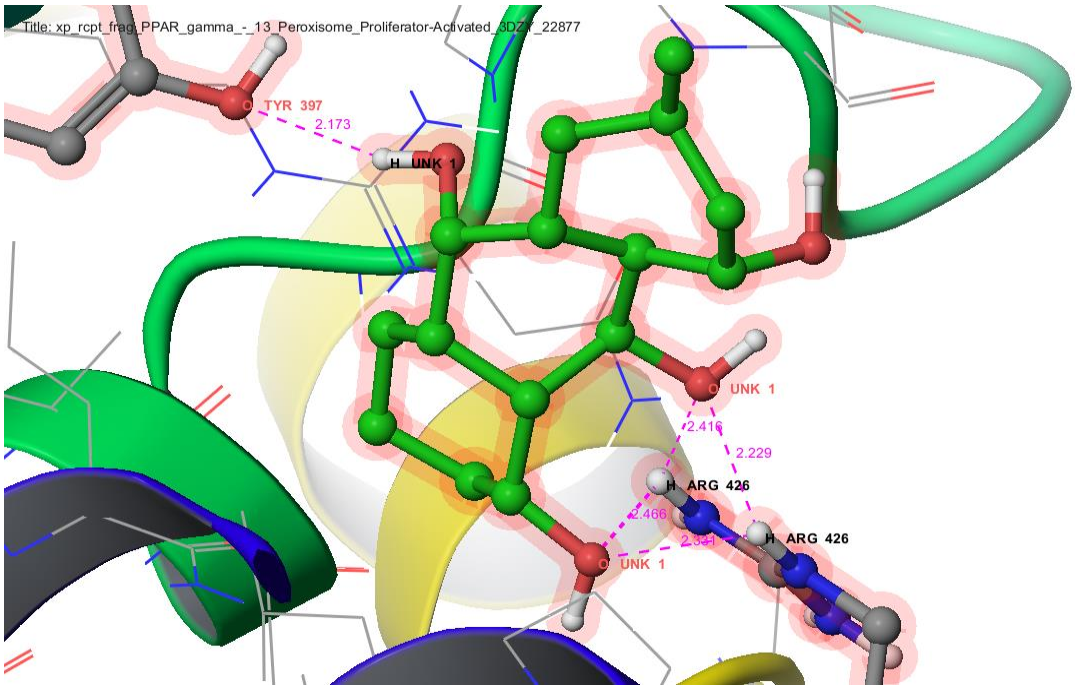

Figure 2: PPAR gamma with Chrysophanol

Peer review under responsibility of Life Science Informatics Publications
2017 May- June RJLBPCS 3(1) Page No.38

4. CONCLUSION

Our finding suggests both the components of *R.emodi* could serve as a PPAR gamma agonists. These findings are significant not only for the elucidation of herbal anti-diabetic mechanism but also for the development of novel PPARs agonists in diabetes therapy. Our finding confirms that chrysophanol and emodin is a novel agonists of PPAR ϒ, it can be used as a diabetic agent to treat type 2 diabetes.

CONFLICT OF INTEREST

The authors have no conflict of interest.

REFERENCES

1. Robert K. Semple., Krishna, V., Chatterjee, K., and Stephen O'Rahilly. PPARγ and human metabolic disease. The Journal of Clinical Investigation, 2006; Vol 116 (3): 581 – 589.
2. Willson, T.M., Lambert, M.H., and Kliewer, S.A. Peroxisome proliferator-activated receptor gamma and metabolic disease. Annu Rev Biochem, 2001; Vol 70:341–367.
3. Renaud, J.P., and Moras, D. Structural studies on nuclear receptors. Cell Mol Life Sci, 2000; Vol 57:1748–1769.
4. Laudet, V., and Gronemeyer, H. The Nuclear Receptor Fact Book, London; AcademicPress 2002.
5. Staels, B., and Fruchart, J.C. Therapeutic roles of peroxisome proliferatoractivatedreceptor agonists. Diabetes, 2005; Vol 54:2460–2470.
6. Ostberg Tove., Stefan Svensson., and Goran Selen. A New Class of Peroxisome Proliferator-activated Receptor Agonists with a Novel Binding Epitope Shows Antidiabetic Effects. J. Biol. Chem, 2004; Vol 279: 41124-41130.
7. Bateman,A., Coin, L ., Durbin,R ., Finn, R.D., Hollich,V., Griffiths-Jones, S. The Pfam protein families database. Nucleic acids research, 2004; vol (32): 138- 141.
8. Shen, P., Liu, M.H., Ng, T.Y., Chan, Y.H., Yong, E.L. Differential effects of isoflavones, from *Astragalus membranaceus* and *Pueraria thomsonii*, on the activation of PPAR-α, PPAR-γ, and adipocyte differentiation *in vitro.* J Nutr, 2006; Vol 136:899.
9. Jianfeng Xue., Wenjun Ding., and Yan Liu. Anti-diabetic effects of emodin involved in the activation of PPARγ on high-fat diet-fed and low dose of streptozotocin-induced diabetic mice. Fitoterapia, 2010; Vol 81 : 173–177.
10. Ying Ma .,Shu-Qing Wang.,Wei-Ren Xu., Run-Ling Wang., and Kuo-Chen Chou. Design Novel Dual Agonists for Treating Type-2 Diabetes by Targeting Peroxisome Proliferator-Activated Receptors with Core Hopping Approach. PLOS One, 2012; Vol 7(6): 1-9.