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INSILICO IDENTIFICATION OF POTENT PPAR AGONISTS FROM *Rheum Emodi* PLANT COMPOUNDS

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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.

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 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.

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

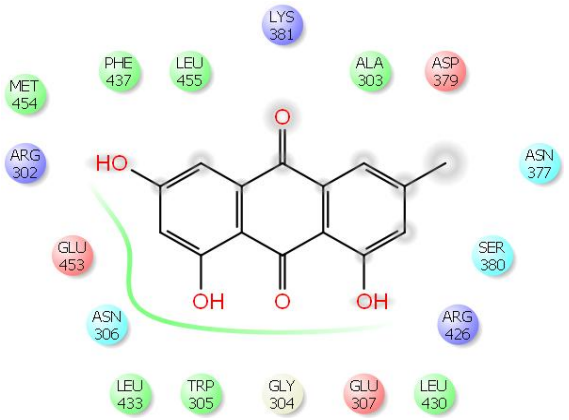
high enrichment across a diverse range of receptor types. Software used for docking is Glide Schrodimger Suite 2012.

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 32, 33).** 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 γInteraction with Emodin

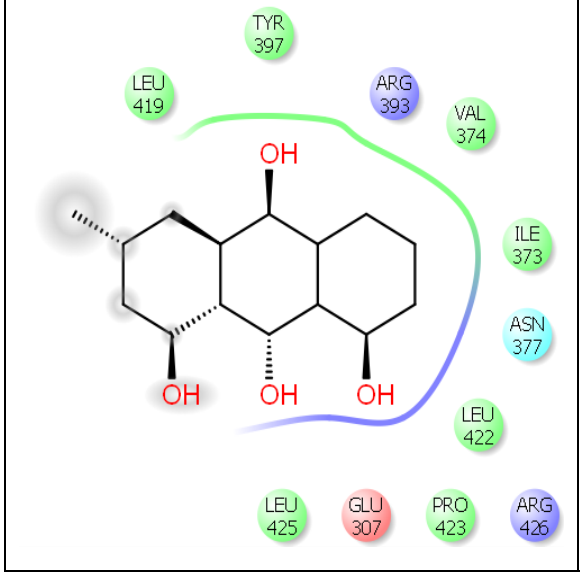
Protein complex	Amino acid	Protein atom	ligand atom	Bond length	Terminii	No of hydrogen bonds	G score
PPARϒ and Emodin	ARG 302	H	O	2.307	Carboxy	2	- 4.23
	MET 454	O	H	1.867	Carboxy		



PPAR receptors interaction with emodin that were created and observed in the energy space created in glide E model resulted in a complex sharing 2 covalent bond (σ bond) between atom types from enzyme and ligand atom. with the reference of the total hydro-oxy bond length 2.86 A^0 (260 picometer based on optimized potentials for liquid simulations 2010 force filed compatibility), the results indicate the oxygen atom from emodin formed 1 σ-bond which is optimized symmetrical (in the energy space alloted) with respect to rotation about the bond axis with Proteins. Hydrogen atom from ARG 302 with bond distance of 2.3.7 A^0 with the hydrogen acceptor from protein atom. Another single oxy-hydro group interacting together and forming hydrogen atom between MET 454th proteins. Oxygen atom with hydrogen atom from ligand in the distance of 1.867 A^0. The partial inference from this molecular docking stating that bond distances are within the molecular mechanics property.

Table 2: Peroxisome Proliferator-Activated Receptor γ Interaction with Chrysophanol

Protein complex	Amino acid	Protein atom	ligand atom	Bond length	Terminii	No of hydrogen bonds	G score
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		



PPAR receptors interaction with chrysophanol that were created and observed in the energy space created in glide E model resulted in a complex sharing a total of 5 covalent bond (σ bond) between atom types from enzyme and ligand atom. With the reference of the total hydro-oxy bond length 2.86 A^0 (260 picometer based on optimized potentials for liquid simulations 2010 force filed compatibility), the results indicate the oxygen atom from chrysophanol formed only a single σ-bond which is optimized symmetrical (in the energy space alloted) with respect to rotation about the bond axis with proteins. Hydrogen atom from TYR 397 with bond distance of 2.173 A^0 with the hydrogen acceptor from protein atom. The oxy-hydro group interactions were together and formed with the hydrogen atom between ARG 426th proteins. Oxygen atom with hydrogen atom from ligand

	in the distances of 2.416 A^0, 2.229 A^0, 2.466 A^0 and 2.331 A^0. The partial inference from this molecular docking stating that bond distances are within the molecular mechanics property.

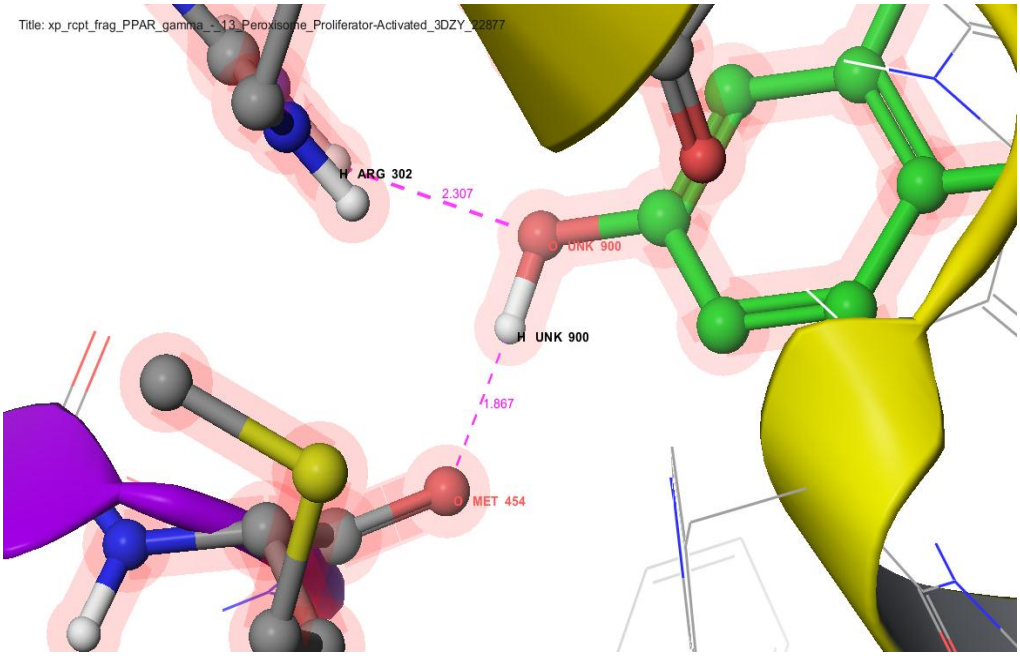


Figure 1: PPAR gamma with Emodin

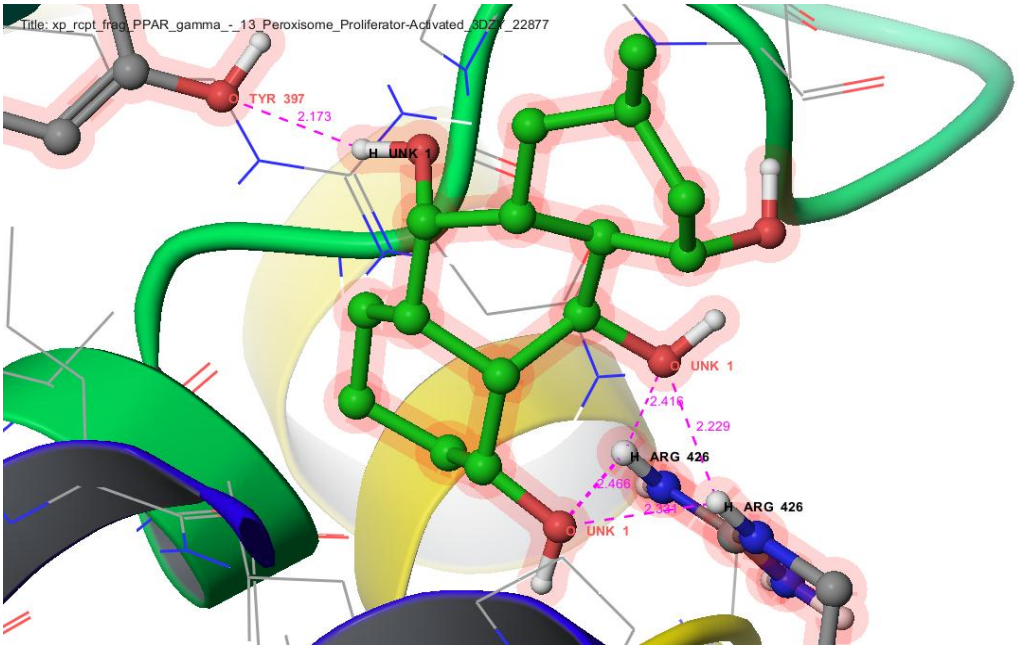


Figure 2: PPAR gamma with Chrysophanol

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.

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