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RESEARCH ARTICLE

A POTENT PLANT COMPOUND FROM *MANGIFERA INDICA* TO TREAT DIABETES

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ABSTRACT

Type 1.5 diabetes also known as latent autoimmune diabetes in adults (LADA) is an important form of diabetes which occurs in about 10% of patients classified as type 2 diabetes and not initially requiring insulin. β- cell dysfunction in type 1.5 diabetes is caused mainly by Glutamic acid decarboxylase antibody (GADA). β- cell stress results in an induction of Heat shock protein 90 (Hsp90) expression, where Hsp 90 is a regulator of Class II antigen processing and presentation. *In silico* docking studies and drug likeliness analysis have shown that docking target protein Hsp 90 α with the ligand mangiferin had a protective role against autoimmune destruction. This study paves way for treating the autoimmune diabetes at the immunity level.

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INTRODUCTION

Diabetes for the whole world is not an epidemic anymore but has turned into pandemic (Lal *et al.,* 2009). Diabetes currently afflicts 171 million people worldwide (Boden and Taggart, 2009). Type 1.5 diabetes also known as latent autoimmune diabetes in adults (LADA) is an important form of diabetes although it is frequently under estimated (Mayer *et al.,*2007). Type 1.5 diabetes occurs in about 10% of patients classified as type 2 diabetes and not initially requiring insulin (Agardh *et al.,* 2005). Type 1.5 diabetics are phenotypic ally similar to type 2 diabetic patients but they are also positive for the autoantibody commonly seen in type 1 diabetes (Stenstrom *et al.,* 2005). There is no established therapeutic intervention for patients with LADA so far and they are currently treated as patients with type 2 diabetes (Chitra and Jeyanthi, 2006). Auto immunity and insulin resistance co-exist in type 1.5 diabetes and the contribution of these factors seems to be reflected in GADA titres (Calsolari *et al.,* 2008). Antibodies to GAD65 (GADA) are considered highly predictive humoral markers of type 1.5 diabetes (Villalba *el al.,* 2007). In auto immune diabetes, β- cell stress results in an induction of Heat shock protein 90 (HSP 90) expression (Kunisawa and Shastri, 2006).

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Recent studies have implicated HSP 90 as a regulator of Class II antigen processing and presentation. As Hsp90 is considered a key component of immune function, its inhibition has become an important target for disease therapy (Bae *et al.,* 2007). *In vitro* studies have shown that the inhibition of HSP 90 by pharmacological agents decrease presentation of both exogenous and endogenous GAD by Class II molecules (Houlihan *et al.,* 2009). Mangiferin, a major C-glucosylxanthone from *M. indica* stem bark, leaves, heartwood, roots and fruits occurs widely among different angiosperm families and ferns. Mangiferin was reported to show pharmacological activities namely antioxidant, immunomodulatory, anti-allergic, anti-inflammatory, antidiabetic and lipolytic properties, supporting the numerous traditional uses of the plant (Wauthoz *et al.,* 2007). Modern approaches to find new leads for therapeutic targets are increasingly based on 3-dimensional information about receptors. An effective way to predict the binding structure of a substrate in its receptor is docking studies which has been used in many applications (Sengupta *et al.,* 2007). In the present study, an *in silico* approach has been carried out to study the inhibitory effect of mangiferin on HSP 90 α protein and to study the drug likeliness of this compound.

MATERIALS AND METHODS

The structure of the target protein HSP 90 α protein complexed with 1-4 - [(2r) -1- (5-chloro-2,4 – dihydroxybenzoyl)

pyrrolidin – 2 - yl] benzyl} -3,3 -difluoropyrrolidinium complex with the protein databank identification number (PDB ID : 3HEK) was retrieved from PDB (www.pdb.org). The structure of mangiferin with the identification number CID5281647 was downloaded from the Pubchem compound database (www.pubchem.org). Docking was done using GLIDE module of Schrodinger version 7.5, drug likeliness was analysed by using Lipinski drug filter of the Supercomputing Facility for Bioinformatics and Computational Biology and the drug likeliness and drug non likeliness of the plant compound mangiferin was compared using the tool Molsoft .

Protein Preparation

OPLS-AA force field (Optimized Potential for Liquid Simulations for All Atoms) aids to perform Glide (Schrodinger) calculations .Energy minimization using OPLS-AA force field in the protein preparation wizard and refinement was carried out until the average root mean square deviation of the non-hydrogen atoms reached 0.3Aº using default settings, Site points were generated followed by generation of the grid displaying the active site with an enclosing box at the centroid of the workspace.

Ligand Preparation

The ligand structure was assigned an appropriate bond order using ligPrep module of Schrodinger. Since the crystal structure contains only one ligand structure but there is a chance that one of the tautomeric forms interacts more strongly with the binding site relative to the other forms, ligprep module generates tautomers all of the other possible tautomeric states of one inhibitor. The ligand mangiferin was prepared for docking.

Docking using Glide

The Glide SP (Standard Precision), a ligand docking program of the software Schrodinger version 7.5 used in the present study for predicting protein-ligand binding modes and ranking ligands via high-throughput virtual screening utilizes scoring functions SP Glide Score, to rank-order compounds. The docking process involves a conformational search for a compound which complements a target binding site, with the aim of identifying the best matching binding pose. The Glide docking algorithm performs a series of hierarchical searches for locations of possible ligand affinity within the binding site of a receptor. The stability of the docked ligand–protein complex is due to hydrogen bonding and van der Waals Interactions. The glide score, glide energy value, H-bonds and vander Waals contacts (good, bad and ugly) to the receptor were visualized in the using default settings to analyze the binding modes of the ligands to receptor .

Finding drug likeliness using Lipinski drug filter

The ligand mangiferin used in the present study was subjected to Lipinski rule screening using the tool Lipinski drug filter of the Supercomputing Facility for Bioinformatics and Computational Biology (http://www.scfbio-iitd.res.in/utility/LipinskiFilters.jsp) according to which prediction of high probability of success or failure is based on drug likeness for molecules complying with 2 or more of the rules namely-molecular mass less than 500 dalton, high lipophilicity (expressed as Log P less than 5),less than 5 hydrogen bond donors, less than 10 hydrogen bond acceptors and molar refractivity should be between 40-130.

Comparing drug likeliness and drug non likeliness using Molsoft tool

The drug likeliness and drug non likeliness of the plant compound mangiferin was compared using the tool Mol soft (http://www.rdchemicals.com/chemistry-software/molsoft.html).

RESULTS

Protein Preparation

The complex 1-4 - [(2r) -1- (5-chloro-2,4 – dihydroxybenzoyl) pyrrolidin – 2 - yl] benzyl} -3,3 –difluoropyrrolidinium complex was removed from the receptor protein Hsp 90 α, water molecules were removed , site points were generated and grid was generated displaying the active site with an enclosing box at the centroid of the workspace.

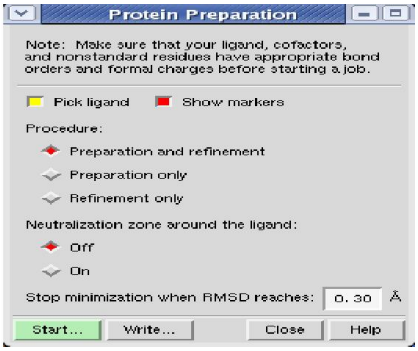


Figure 1. Protein preparation wizard used for protein preparation and refinement

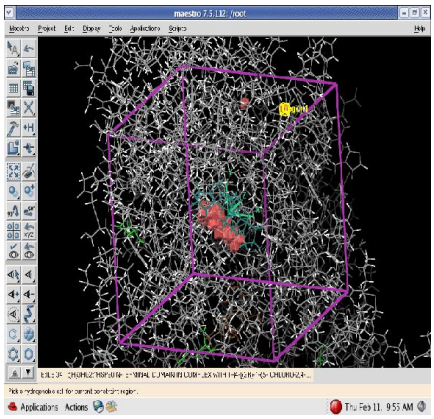


Figure 2. Grid generation in the Hsp 90 α

Ligand Preparation

Ligand was prepared using ligprep module. For the ligand mangiferin used in the present study, the best tautomeric form was generated.

Table 1. Molecular details of mangiferin

Ligand	Drug / Compound identification number	Molecular formula	Molecular weight
Mangiferin	CID5281647	$C_{19}H_{18}O_{11}$	422.34

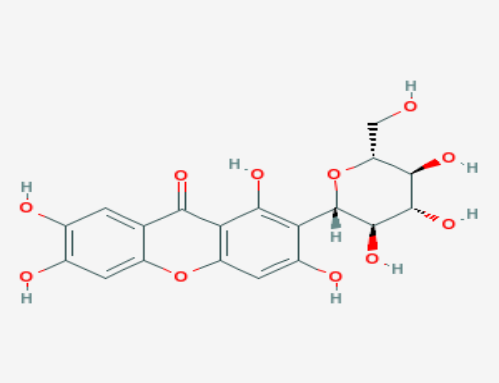


Figure 3. Chemical structure of mangiferin

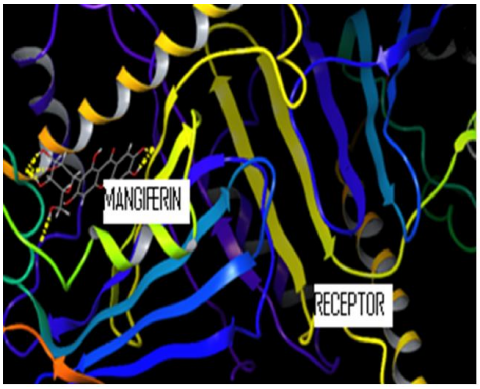
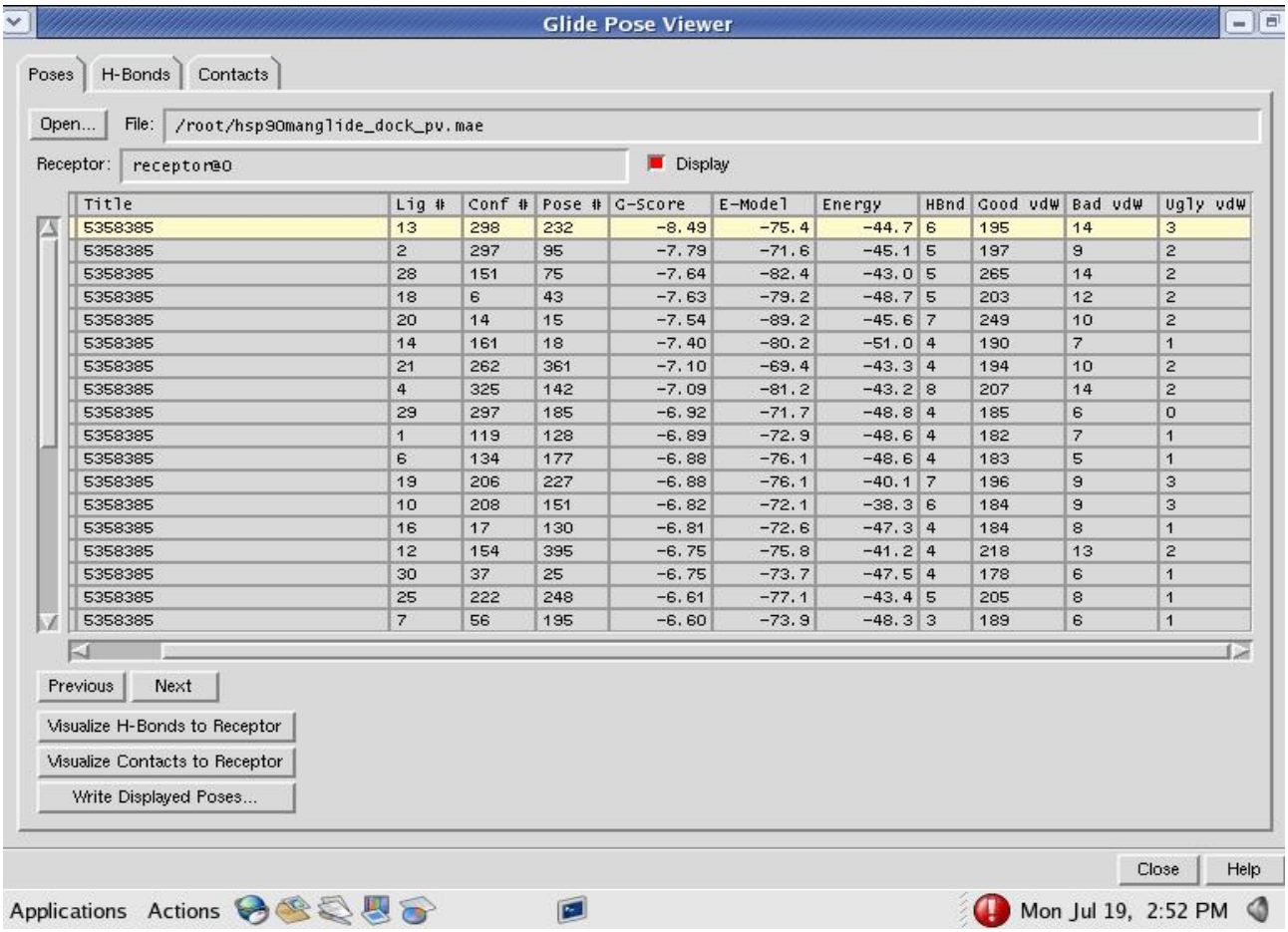


Figure 4. Docking of hsp90 with mangiferin



Title	Lig #	Conf #	Pose #	G-Score	E-Model	Energy	HBnd	Good vdW	Bad vdW	Ugly vdW
5358385	13	298	232	-8.49	-75.4	-44.7	6	195	14	3
5358385	2	297	95	-7.79	-71.6	-45.1	5	197	9	2
5358385	28	151	75	-7.64	-82.4	-43.0	5	265	14	2
5358385	18	6	43	-7.63	-79.2	-48.7	5	203	12	2
5358385	20	14	15	-7.54	-89.2	-45.6	7	249	10	2
5358385	14	161	18	-7.40	-80.2	-51.0	4	190	7	1
5358385	21	262	361	-7.10	-69.4	-43.3	4	194	10	2
5358385	4	325	142	-7.09	-81.2	-43.2	8	207	14	2
5358385	29	297	185	-6.92	-71.7	-48.8	4	185	6	0
5358385	1	119	128	-6.89	-72.9	-48.6	4	182	7	1
5358385	6	134	177	-6.88	-76.1	-48.6	4	183	5	1
5358385	19	206	227	-6.88	-76.1	-40.1	7	196	9	3
5358385	10	208	151	-6.82	-72.1	-38.3	6	184	9	3
5358385	16	17	130	-6.81	-72.6	-47.3	4	184	8	1
5358385	12	154	395	-6.75	-75.8	-41.2	4	218	13	2
5358385	30	37	25	-6.75	-73.7	-47.5	4	178	6	1
5358385	25	222	248	-6.61	-77.1	-43.4	5	205	8	1
5358385	7	56	195	-6.60	-73.9	-48.3	3	189	6	1

Figure 5. Glide pose viewer displaying the glide score for mangiferin

Table 2. Docking result of mangiferin for HSP 90 α

Ligands	Glide score	Glide energy	No. of hydrogen bonds	Aminoacids involved in Interaction
Mangiferin	-8.49	-44.7	6	Lys 112, Asp 93 and Ile110

Receptor – ligand docking using Glide

Docking procedures basically aim to identify the correct conformation of ligands in the binding pocket of a protein and to predict the affinity between the ligand and the protein. It is a process by which two molecules fit together in a 3-dimensional space .Docking algorithm based on the tetrahedral grid model of proteins allows a more precise description of shape complementarity.

The Glide SP (Standard Precision), a ligand docking program of the software Schrodinger version 7.5 used in the present study predicts protein-ligand binding modes and ranks ligands via high-throughput virtual screening utilizing scoring functions SP Glide Score, to rank-order compounds.

Finding drug likeliness using Lipinski drug filter

In the present study the ligand- mangiferin satisfied four rules establishing drug likeliness of the ligand.

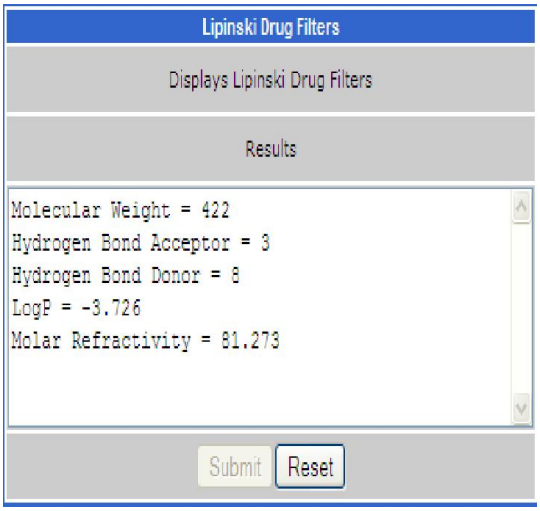


Figure 6. Results of Lipinski drug filters for radanamycin

Table 3. Lipinski drug filter result of mangiferin

Ligands	Molecular weight	Hydrogen bond donor	Hydrogen bond acceptor	LogP	Molecular refractivity
Mangiferin	422	8	3	- 3.726	81.273

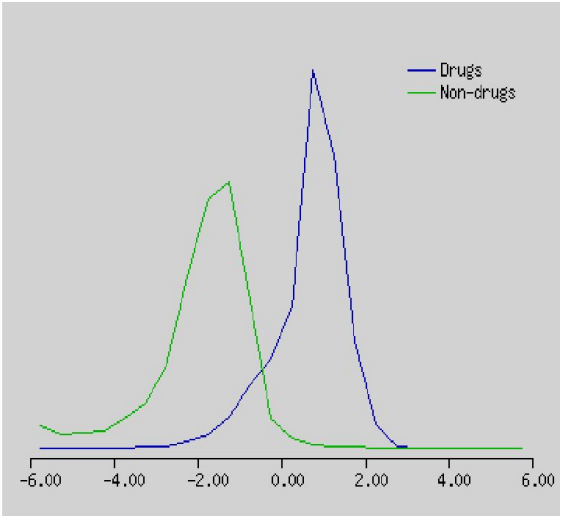


Figure 7. Drug-likeness model score

The result of the Molsoft shows that the drug likeliness score for mangiferin is 0.50 and from the figure it is proved that the drug likeliness is comparatively greater than the drug non-likeliness.

DISCUSSION

The ligand molecule mangiferin was docked with the target protein Hsp 90 α involving six hydrogen bonds. Mangiferin interacted with the HSP 90 α with a glide score value of -8.49. The amino acids found to be involved in interaction were Lys 112, Asp 93 and Ile110. Drug likeliness score was found to be 0.50. In the present study the ligand molecule mangiferin satisfied more four rules of Lipinski's rule of five predicting high probability of success to show drug likeliness. Drug likeliness was also found to be more.

Conclusion

Thus the *insilico* method adopted in the present study helped in identifying the plant compound mangiferin to be a potent ligand using the commercial software and online tools for the pandemic disorder diabetes. This method not only reduces the time and cost in designing a drug, in analyzing the drug likeliness before it enters the clinical trials but also throws light into the natural bio world for being used to treat the disorder of the third world- diabetes.

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