

## Research Article



## Hemidesmus indicus Plant Derived Compounds as Aldose Reductase Inhibitors – A Molecular Docking Study

Shravan Kumar Gunda<sup>1\*</sup>, Seshagiri Bandi<sup>1</sup>, Sahithi P<sup>2</sup>

<sup>1</sup>Bioinformatics Division, Osmania University, Hyderabad, Telangana State, India.

<sup>2</sup>Biotechnology Division, Osmania University, Hyderabad, Telangana State, India.

\*Corresponding author's E-mail: gunda14@gmail.com

Accepted on: 13-07-2015; Finalized on: 31-08-2015.

### ABSTRACT

The primordial role played by Aldose reductase in type 2 Diabetes is widely documented and the plant as *Hemidesmus indicus* is known to be an important medicinal plant of numerous uses with special interest lying in its derived secondary metabolites to inhibit Aldose reductase activity. In this study we performed a protein ligand interaction study of 40 molecules from *Hemidesmus indicus* with Aldose reductase as the target protein. We describe docking of 40 compounds from *Hemidesmus indicus* into the 3D structure of 1H4G of Homo sapiens using FlexX of which molecular docking and scoring of top four compounds namely Vanillin, 2-hydroxy-4-methoxy benzaldehyde, Hyperoside, Isoquercetin, p-methoxysalicylic aldehyde, Phenylpropanoid were identified as potential inhibitors that showed high binding affinity for Aldose reductase enzyme.

**Keywords:** *Hemidesmus indicus*, Aldose reductase, FlexX docking.

### INTRODUCTION

*Hemidesmus* belongs to the family Asclepiadaceae. It is used as tonic, demulcent, diuretic, purgative, diaphoretic, and also a blood purifier<sup>1,2</sup>.

*Hemidesmus indicus* is a perennial, prostrate, twining shrub which is known for its medicinal uses against bronchitis, syphilis, leucorrhoea, chronic rheumatism, leprosy, skin diseases and urinary diseases besides being used as an antidiabetic, antidiarrhoeal, anticancer, antipyretic in folk medicines<sup>3</sup>.

The Common name for *Hemidesmus indicus* is Anantmul, and also called as Indian sarsaparilla. The plant is commonly used for the treatment of cardiovascular and gastrointestinal disorders.

The Asclepiadaceae family is known for its affluent compounds such as Pregnane, cardiac glycosides, triterpenes and pregnane glycosides<sup>4,5,6</sup> and is also known for its many aromatic secondary metabolites like phenylpropanoids, benzoates, flavonoids, catechins and lignin.

FlexX Molecular docking studies were carried out for *Hemidesmus indicus* plant derived compounds to identify protein ligand interactions.

Long term complications are main cause of mortality and morbidity in diabetic patients. Diabetes mellitus is a common disease with many complications such as cardiac dysfunction, neuropathy, atherosclerosis, nephropathy and retinopathy<sup>7</sup>.

Several metabolic factors observed in diabetic vasculopathy. Aldose reductase belongs to aldo-keto reductases super family. It is the rate limiting enzyme in

the polyol pathway and reduces glucose to sorbitol utilizing NADPH as a cofactor<sup>8</sup>.

### MATERIALS AND METHODS

#### Selection of molecules for docking

A set of 40 *Hemidesmus indicus* derived plant compounds<sup>8,9</sup> were used for the docking studies. All the molecules were sketched in Silicon Graphics O2-Tripes SYBYL 6.7<sup>10</sup> software and were minimized after adding Hydrogens to their most appropriate conformation using the Powell method and Gasteiger - Huckel charges.

#### Target protein preparation

The X-ray crystal structure of "Chain A, Oligosaccharide-Binding to Family 11 Xylanases: Both Covalent Intermediate and Mutant-Product Complexes Display 2,5b Conformations at The Active-Centre" (PDB ID: 1H4G) was retrieved from PDB database in a monomeric structure configuration. The protein PDB was co crystallized with FXP (co-crystallized inhibitor) and water molecules, but in order to do FlexX docking all the water molecules must be removed so as to remove redundancies for ligand docking. Implicit hydrogen atoms were added to the structure complex using the biopolymer module of the SYBYL6.7 so as to satisfy their valancies.

#### Docking studies

FlexX<sup>11</sup> is a fragment based method. FlexX handles the flexibility of the ligand by decomposing the ligand into small fragments and performs the incremental construction algorithm procedure directly inside the protein active site. It allows ligand flexibility while keeping the protein rigid. The ligand core is selected such that it has most potential interaction groups and the



fewest alternative conformations. FlexX scoring function is a modification of Bohm's function developed for the denovo design program LUDI. Computational molecular docking was carried out using FlexX option in Sybyl 6.7 software and the compounds were docked sequentially into the active site of 1H4G using the FXP as the reference molecules, to provide the interaction between the ligand and the receptor. The sketched molecules were minimized using Tripos force fields by adding Gasteiger-Huckel charges. Multiligand docking was used for the structures using FlexX module of Sybyl. Receptor description file (RDF) was created within the area of 6.5Å around the co-crystallized ligand and formal charges were assigned for all molecules. Customization was carried out while including the most important amino acids that are known to form hydrogen bonds like Glu94, Tyr85, Arg129, Pro133, Arg49 and Glu17. Formal charges were assigned to all the molecules and were docked. The clustering of generated models was carried out for both base placement and adding fragment steps.

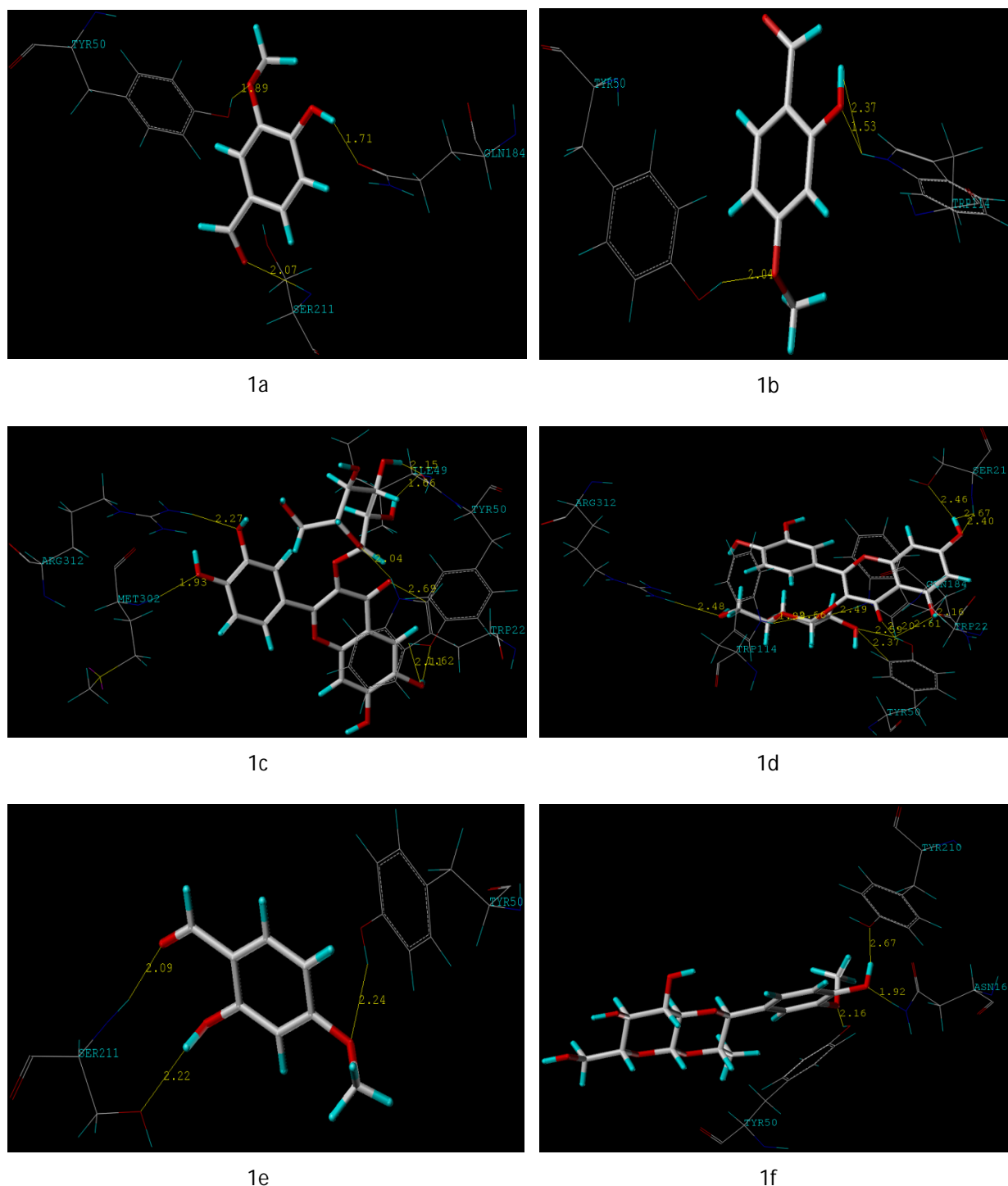
FlexX scoring function was used and as FlexX ignores hetero atom records like metal atoms, the bound ligand and the water molecules in the PDB file during docking study the PDB file was manually tweaked to remove the before said information for the enrichment of docking study.

## RESULTS AND DISCUSSION

*Hemidesmus indicus* plant compounds were docked with the Aldose reductase protein structure (PDB ID: 1G4H) and the docking scores for all the compounds were recorded. Active site of 1H4G offers different binding modes for Docking studies were performed for all these molecules (Vanillin, 2-Hydroxy-4-methoxy benzaldehyde, Hyperoside, Isoquercetin and p-methoxysalicylic aldehyde, phenylpropanoid) into the active site of 1H4G complexed with FXP. As these compounds are known to produce antidiabetic activity by binding to Aldose reductase inhibitors. Some important interactions operating at the molecular level, Tyr50 plays a important role in binding all the molecules. Molecule p-methoxysalicylic aldehyde conformer shows more dock score (-20.2) followed by 2-Hydroxy-4-methoxy benzaldehyde(-18.6), phenylpropanoid(-18.1), Vanillin (-17.9), Hyperoside(-17.8) and Isoquercetin (-16.4). Isoquercetin formed more number of H-bond interactions with Trp22, Tyr50, Trp114, Gln184, Ser211 and Arg312 respectively and is shown in fig 1a, 1b, 1c, 1d, 1e, 1f. It is probably because of interactions with these residues, the scores are higher for these molecules. All the ligands are showing interactions with Tyr50. The dock score of the top six compounds along with their interacting amino acids are shown in the table 1.

**Table 1:** *Hemidesmus indicus* plant derived compound names with their interacting amino acids, distance and their dock score.

Compound Name	Interacting amino acid	Distance (Å)	Dock Score
Vanillin	Tyr50	1.89	-17.9
	Gln184	1.71	
	Ser211	2.07	
2-Hydroxy-4-methoxy benzaldehyde	Tyr50	2.04	-18.6
	Trp114	1.53, 2.37	
Hyperoside	Trp22	2.04	-17.8
	Ile49	1.66, 2.15	
	Tyr50	1.62, 2.11, 2.69	
	Met202	1.93	
	Arg312	2.27	
Isoquercetin	Trp22	2.16	-16.4
	Tyr50	2.20, 2.37, 2.59, 2.61	
	Trp114	1.99, 2.66	
	Gln184	2.49	
	Ser211	2.40, 2.46, 2.67	
	Arg312	2.48	
p-methoxysalicylic aldehyde	Tyr50	2.24	-20.2
	Ser211	2.09, 2.22	
Phenylpropanoid	Tyr50	2.16	-18.1
	Asn163	1.92	
	Tyr210	2.67	



**Figure (1a):** Vanillin **(1b):** 2-Hydroxy-4-methoxy benzaldehyde **(1c):** Hyperoside **(1d):** Isoquercetin **(1e):** p-methoxysalicylic aldehyde and **(1f):** phenylpropanoid compounds with their interactions in the active site of 1G4H.

## CONCLUSION

Molecular docking studies using FlexX software has been carried out in SYBYL software to explore the binding mechanism of Hemidesmus indicus derived plant compounds against Aldose reductase. Vanillin, 2-Hydroxy-4-methoxy benzaldehyde, Hyperoside, Isoquercetin, p-methoxysalicylic aldehyde and phenylpropanoid molecules shows better with Aldose reductase based on FlexX score and interaction with the active site residues in comparison with the existing molecule. This information

provides insight to the consideration of structural requirement for the potential drug candidates against Aldose reductase in diabetes.

## REFERENCES

1. Austin A. A review of Indian sarsaparilla, Hemidesmus indicus (L.) R. Br. *J Biol Sci*, 8, 2008, 1–12.
2. George S, Tushar KV, Unnikrishnan KP, Kashim KM, Balachandran I. Hemidesmus indicus (L.) R. Br. A review. *J Plant Sci*, 3, 2008, 146–156.



3. Kirtikar KR, Basu BD. Indian medicinal plants, International Book Distributors, India. 1984.
4. Deepak D, Srivastav S, Khare NK, Khare A. Cardiac glycosides. Progress in the Chemistry of Organic Natural Products, 69, 1996, 71-148.
5. Deepak D, Srivastav S, Khare A. Pregnane glycosides. Progress in the Chemistry of Organic Natural Products, 71, 1997a, 169-325.
6. Oberai K, Khare MP, Khare A. A pregnane ester diglycoside from *Hemidesmus indicus*. Phytochemistry, 24, 1985, 2395–2397.
7. Sowers JR, Epstein E, Frohlich ED. Hypertension and cardiovascular disease: an update. Hypertension, 37, 2001, 1053-1105.
8. Saraswat M, Muthenna P, Suryanarayana P, Petrash JM, Reddy GB. Dietary sources of aldose reductase inhibitors: prospects for alleviating diabetic complications, Asia pac J clin Nutr, 17(4), 2008, 558-565.
9. Kundu A, Mitra A. Flavoring Extracts of *Hemidesmus indicus* Roots and *Vanilla planifolia* Pods Exhibit *In vitro* Acetylcholinesterase Inhibitory Activities. Plant Foods Hum Nutr, 68(3), 2013, 247-253.
10. SYBYL 6.7, Tripos Associates Inc., 1699 S. Hanley Rd., St. Louis, MO 631444, USA.
11. Rarey M, Kramer B, Lengauer T, Kleb GA, Fast flexible docking method using an incremental construction algorithm, J. Mol. Biol, 261, 1996, 470–489.

**Source of Support:** Nil, **Conflict of Interest:** None.

