



## Molecular Docking Studies of *Grewia umbellifera* Plant Derived Compounds

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### ABSTRACT

The primordial role played by Aldose reductase in type 2 Diabetes is widely documented and the plant as *Grewia umbellifera* 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 *Grewia umbellifera* with Aldose reductase as the target protein. We describe docking of 40 compounds from *Grewia umbellifera* 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:** *Grewia umbellifera*, Aldose reductase, FlexX docking.

### INTRODUCTION

Molecular docking is the technique employed for predicting and analyzing the interactions between protein receptors and ligands. It provides most detailed possible view of drug receptor interactions and also has created a new rational approach to drug

design. Considering the high incidence of diseases, there is always a demand to find molecules for treatment. There are around 200 million people with diabetes and the number is expected to rise to almost 350 million by 2025. The global epidemic of diabetes and its impact on ocular



complications, particularly diabetic cataract is a serious concern. Although strict glycemic control is expected to prevent diabetic complications, perfect glycemic management of secondary complications. Thus inhibition of ALR2 is one of the targets that need to be investigated in the light of diversified physiological functions of ALR2.

Aldose reductase (EC: 1.1.1.21; NADPH oxidoreductase, ALR2) belongs to the aldo-keto reductase (AKR) superfamily and catalyzes the NADPH-dependent reduction of a wide variety of aldehydes and ketones to their corresponding alcohols. ALR2 is a cytosolic enzyme and is widely distributed in eye lens, retina, kidney, adrenal gland and various reproductive organs. In the presence of NADPH, the enzyme catalyzes the rate-limiting step in the polyol pathway where it converts glucosetosorbitol [1,2.] Subsequentlysorbitol dehydrogenase catalyzes the conversion of sorbitol to fructose thus constituting the polyol pathway. Activation of the polyol pathway in hyperglycemia leads to

control is not always possible. Hence, agents that can prevent diabetic complications, irrespective of glycemic control, need critical evaluation in the perturbation of metabolic homeostasis, particularly depletion of NADPH and accumulation of sorbitol in tissues where glucose uptake is not dependent on insulin. Thus increased ALR2 mediated flux of glucose into the polyol pathway in target tissues such as eye lens has been implicated as a major cause in the etiology of diabetic cataract. Because sorbitol does not easily cross cell membranes and its subsequent conversion to fructose is slow, it accumulates inside the cell, resulting in altered. osmotic pressure and redox state of pyridine nucleotides (increased NADH/NAD ratio). Compelling evidence for this hypothesis has come from numerous animal models, mainly rodents [3], where administration of ALR2 inhibitors (ARI) has been shown to prevent cataract formation.

Grewia umbelliferea is a small tree plant 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 [4]. It is used as tonic, demulcent, diuretic, purgative, diaphoretic, and also a blood purifier [5],

[7-9] triterpenes and pregnane glycosides 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 Grewia umbellifera plant derived compounds to identify protein ligand interactions.

## **MATERIALS AND METHODS**

### **Selection of molecules for docking**

A set of 40 Grewia umbellifera derived plant compounds [10,11] were used for the docking studies. All the molecules were sketched in Silicon Graphics 02-Tripes SYBYL 6.7 software and were minimized after adding Hydrogens to their most

[6]. It belongs to the family Tiliaceae. The Common name for Grewia umbellifera is Anantmul, and also called as Indian sarsaparilla. The Asclepiadaceae family is known for its affluent compounds such as Pregnane, cardiac glycosides,

appropriate conformation using the Powell method and Gasteiger - Huckel charges.

### **Target protein preparation**

The X-ray crystal structure of (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 valencies.



### Docking studies

FlexX [13] 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 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  $6.5\text{\AA}$  around the co-crystallized ligand and formal charges were assigned for all molecules. Customisation 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

fewest alternative conformations. FlexX scoring [13] 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 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

Grewia umbellifera 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 an 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 1, 2, 3, 4, 5 and 6. 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.

## CONCLUSION

Molecular docking studies using FlexX software has been carried out using SYBYL software to explore the binding mechanism of *Grewia umbellifera* derived plant compounds against Aldose reductase. Vanillin, 2-Hydroxy-4-methoxy benzaldehyde, Hyperoside, Isoquercetin, p-methoxysalicylic aldehyde and phenylpropanoid molecules show 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 candidates against Aldose reductase in diabetes.

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**Figures 1-6:** (1) Vanillin (2) - Hydroxy-4-methoxy benzaldehyde (3)Hyperoside (4) Isoquecetin (5) p-methoxysalicylic aldehyde and (6) phenyl propanoid compounds with their interactions in the active site of 1G4H

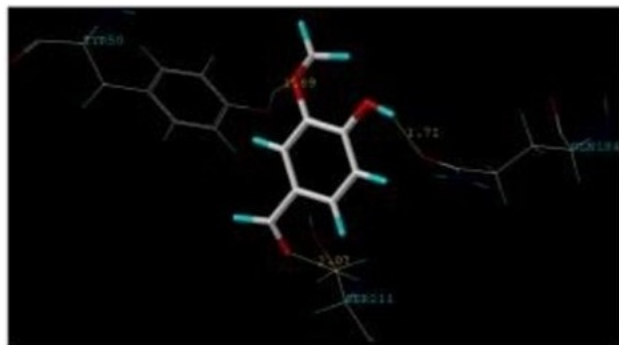


Fig: 1

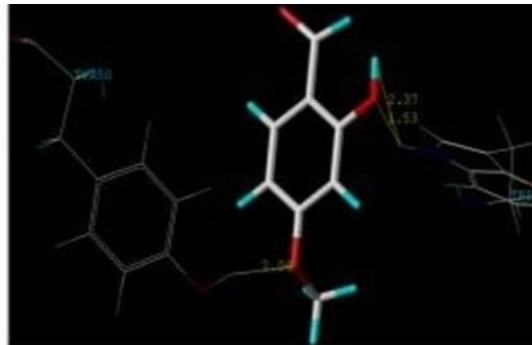


Fig:2

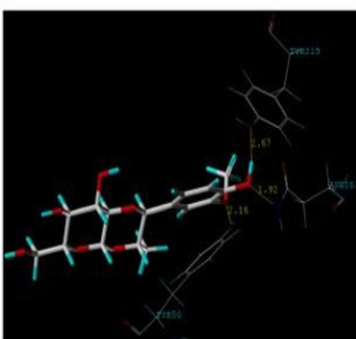
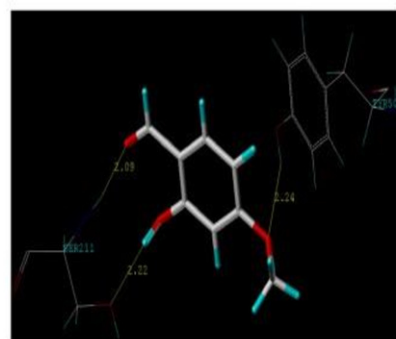
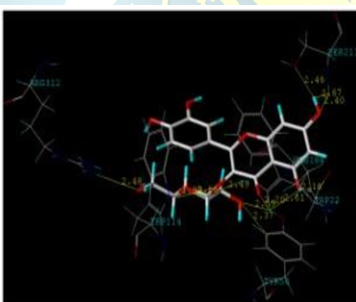
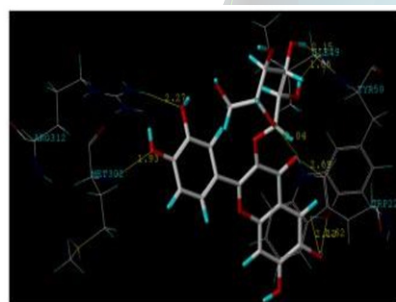


Fig. 3 – 6





Compound name	Interacting amino acid	Distance (Armstrong)	Dock score
Vanillin	Tyr50	1.89	-17.19
	Gln184	1.71	
	Ser211	2.07	
2-hydroxy-4-methoxy benzaldehyde	Trp144	1.53	-18.6
	Trp22	2.37	
Hyperoside	Tyr50	2.11	-17.8
	Met202	1.93	
Isoquercetin	Gln184	2.24	-16.4
	Ser211	2.04	
P-methoxysalicylic aldehyde	Ser211	1.92	-18.1
	Tyr50	2.67	

**Table – 1:** Plant derived compound names with their interacting amino acids, distance and their dock score.