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Review Article

AN OVERVIEW ON DOCKING STUDIES WITH ALDOSE REDUCTASE INHIBITORS

Zeyad Ahmmed Dahan Mohammed[1], **Sayyed Hussain Sajjansab**[1] and PK Zubaidha[2]

[1]Sir Sayyed College of Arts, Commerce and Science, Roshangate, Aurangabad, India

[2]School of Chemical Sciences, SRTM University, Nanded 431606, Maharashtra, India

ABSTRACT

Molecular modeling methods have become integral part of drug discovery programs as they enable study of complex biological and chemical systems and hence design of lead molecules of therapeutic significance. Over the last few decades, it has been routinely and successfully applied in most pharmaceutical and biotech companies for a large number of applications. The activation of the key enzyme Aldose reductase in polyol pathway under hyperglycemic conditions is responsible for the development of late diabetic complications and it is an important drug target. This review provides an update on the docking strategies employed for screening various synthetic and natural aldose reductase inhibitors and provide an overview of the structural features involved in binding within the active site. The docking results reveal that several active constituents of medicinal plants exhibit remarkable aldose reductase activity and they may serve as lead for the development of novel ALRs of therapeutic significance.

Keywords: Aldose reductase, Polyol pathway, Inhibitors, Natural products, Docking studies, Review.

INTRODUCTION

Molecular docking is an essential component in modern drug discovery. with the availability of protein/ nucleic acid data bank, virtual screening, binding site identification, structure function studies and protein protein interaction s are successfully applied in most pharmaceutical companies for a large number of applications. Also docking against homology modeled targets has become possible for more proteins. Type 2 diabetes, one of the major life threatening diseases worldwide continue to progress at an incremental rate every year and most of the research work to control the disease target either enzymes or proteins. Aldose reductase the key enzyme in the polyol pathway gets activated under hyperglycemic conditions and reduces glucose to sorbitol . The enzyme has been attributed to the development of late diabetic complications. [Wong *et al.* 2009] Hence, aldose reductase is an important drug target and their inhibitors are promising therapeutic agents to combat development of late diabetic complications such as as neuropathy, nephropathy, retinopathy, and cataracts. [Shigeta, *et. al* 1990] At present only few drugs are available to treat diabetic complications and development of new selective ALRS are highly desirable. [Sang *et al.*, 2006, Nishimura CY, 1998]. The goal of molecular docking is to predict the interactions between three dimensional structures of interest. Computational docking exploit the concept of molecular complementarity where both physic- chemical properties and shape of the structures contribute to the fit. The docking itself produces only plausible candidate structures and they are ranked by different methods such as scoring functions to identify most likely drug candidate. Computational studies that dock small molecules into the structures of macromolecular targets to evaluate molecular complementarity to the binding site are widely used in lead optimization and hit identification. The structure based ligand discovery focus on screening of compound libraries using molecular docking given the atomic resolution of macromolecule such as

enzyme and hence modulate activity. The advantage would include use of target as template for design of novel ligands different from the existing ones. The docking requires high rate of hit enhancement and it is complementary to the dominant high throughput screening used in pharmaceutical companies. The structure based drug design and screening has led to development of large number of drugs such as HIV protease inhibitors. However, application of these strategies presents significant challenges with regard to the existing scoring schemes.

RECENT ADVANCES IN DOCKING

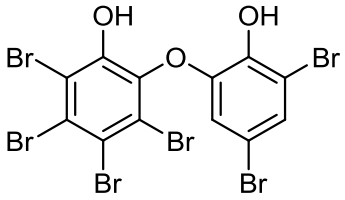
Given the importance of Molecular docking, large number of new algorithms and programs-such as AutoDock, DOCK, Ecepp/ Prodock, FlexX, FLOG, GOLD, GREEN, ICM, LUDI,Pro_LEADS, QXP and SLIDE [Totrov *et al.*2001] have been introduced in the past year, including the EUDOC algorithm[Prendergast *et al.* 2001] SEED [Caflisch *et al.* 2001], and MM . However, Treatment of receptor flexibility remains a major challenge [McCammon *et al.* 2000] and accommodation of receptor conformation and its flexibility make the docking calculation worse. The program FlexE [Flex *et al.* 2001], based on predefined ensemble structure is twofold faster than explicit docking against all conformations. In the Auto Dock program Goodshell and co-workers [Goodsell *et al.* 2002] considered an ensemble of receptor conformations and averaged energy interaction grid was used to represent them [Oshiro *et al.* 2000]. In the SLIDE program, Schnecke and Kuhn [Kuhn *et al.* 2000] opted for optimization of receptor conformation after placement of ligand. Scoring functions for database docking may be roughly categorized under: empirical –regression, force- field methods, knowledge based methods and force- field methods. Although force – field methods are quantitatively reliable for molecular dynamics and thermodynamic integrations, include salvation energies they are prone to produce high magnitude and high error interaction energies while knowledge based and empirical scoring functions derive from pattern of atom contacts observed in structures and binding energies of atom fits respectively. These methods do not calculate overly large interaction energies but suffer from errors due to induction and data from which they are derived. Also, several methods use a generalized Born/ surface area model or continuum electrostatics approximations and they and these continue to be explored [Bashford *et al.* 2001]. Use of partial atomic charges for the ligands improve docking screens [Bayly *et al.* 2000]. Recent improvements in these models [Shakhnovich *et al.* 2000] include balance between polar and non polar interactions[Stahl M, 2000], considering the role of solvent[Klebe *et al.* 2000] , and correcting for intra-ligand contacts in the structures from which the knowledge-based potentials are derived [Muegge I, 2001] Although all the methods give good results and reliable results are achieved by consensus scoring schemes that combine scores from fundamentally different approaches [Walters *et al.* 1999, Rognan *et al.* 2000. Ortiz *et al.* 2001, Jorgensen *et al.* 2001].For many interesting targets, an experimental structure is unavailable and homology modeled structures are used to improve the pharmacokinetic properties of known inhibitors[Lambert *et al.* 2001] and to study structure–activity relationships [Miller *et al.* 2001]. Also modeled structures could be used with *De novo* design methods to develop new inhibitors [Metcalf *et al.* 2000].

Aldose Reductase: Structure

Aldose reductase falls under the super family aldo- keto reductase and brings about catalysis of NADPH - dependent reduction of variety of substrates varying from aldo-sugars to aromatic/aliphatic aldehydes. It is a globular protein, has more than 2,500 atoms with 315 amino acid residues (Molecular weight 35722.21Da). The enzyme folds in the most common motif known for enzymes: the beta/alpha barrel. The eight beta/alpha helix sub units are repeatedly arranged to form the active site of the enzyme in the center. A common fold covers the whole protein structure. The enzyme binding site for the substrate involve Trp20, Tyr48, His110, Trp111, Phe122, Phe115, Met303 and Leu300.

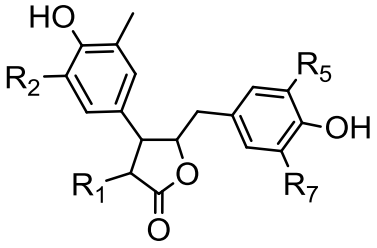
Docking Studies With Aldose Reductase

Docking of polybrominated diphenyl ether a marine natural product studied by Fuente et al [Federico et al. 2003] displays aldose reductase inhibitory activity 17 fold compared to sorbitol.



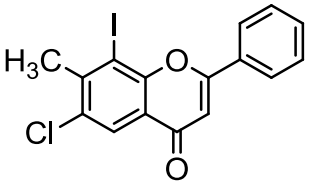
Polybrominated diphenyl ether

Homology modeling, automated docking and energy refinement methods were used to build, the molecular representation of human ALR2 complex with the diphenyl ether and molecular dynamics simulation of chlorobenzene, bromobenzene and fluorobenzene were used to derive AMBER parameters for the halogens. Similar to Zenarestat the inhibitor binding was proposed to cause conformational change. The crucial importance of bromine atom that is responsible for the enhanced activity was studied by free energy perturbation thermodynamic cycle and it was found that the special location of the bromine atom was equivalent to the only bromine atom present in zenarestat. Another marine natural product 2 with potential ARI activity was investigated for binding mode and mechanism by Chengbu Liu *et al* [Zhangyu *et al.* 2009].



Phenolic marine natural product

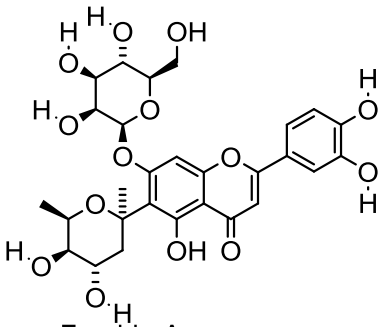
Docking studies of six phenolic inhibitors were studied on hALR2. Considering the physiological environment all the neutral and ionized states were simulated in the study. All the inhibitors were able to form hydrogen bonds with the residues TYR48, HIS110 and TRP111 occupying the active space. The site of binding either through hydroxyl group or lactone ring in the active site seems to be controlled by the bromine atom and both the binding modes were found to be of high stability. The authors point our clearly that ionization mode does play role in stabilizing the complex by electrostatic interactions. Natural products containing flavones moiety are well known to inhibit aldose reductase, along these lines, Gyananath *et al.* [Gyananath *et al.* 2011] studied the docking mode and mechanism of binding of halogen substituted flavones to probe the effect of halogen in binding. Among the flavones investigated, 3-iodo, 4-methyl, 5-chloroflavone exhibit higher binding as compared to other flavones.



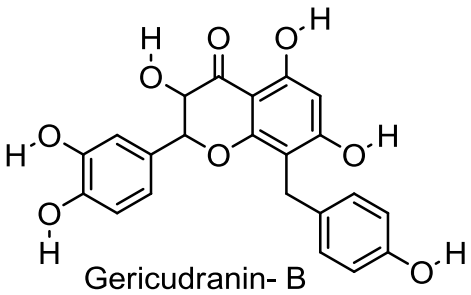
3 iodo 4- methyl 5chloroflavone

Further, studies reveal that the site directed mutagenesis of Val47Ile, Tyr48His, Pro121Phe, Trp219Tyr, Cys298Ala, Leu300Pro, Ser302Arg, and Cys303Asp of the enzyme alters the inhibitory activity. The reliability of the docking studies was validated by correlating the docking scores of known inhibitors and the experimental logIC50 values with regression value of .81.

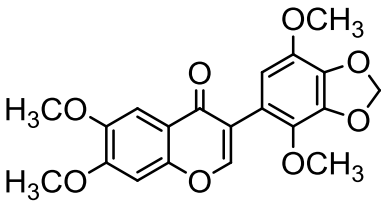
In another study by Muthuswamy et al **[**Muthuswamy *et al.* 2012**],** different flavonoids like Farobin-A, Gericudranin- B, Glaziovianin-A, Rutin, and Xanthotoxin were docked on aldose reductase and compared with epalrestat, a standard well known aldose reductase inhibitor. The selected flavanoids bind well with the ALR with binding energy between -7.91 kcal/mol to -5.08 kcal/mol as compared to the standard (-5.59 kcal/mol). Also, this is supported by intermolecular energy (-9.11 kcal/mol to -8.66 kcal/mol) and inhibition constant (1.58 μM to 187.37 μM) of the ligands.



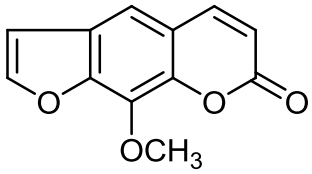
Farobin-A



Gericudranin- B

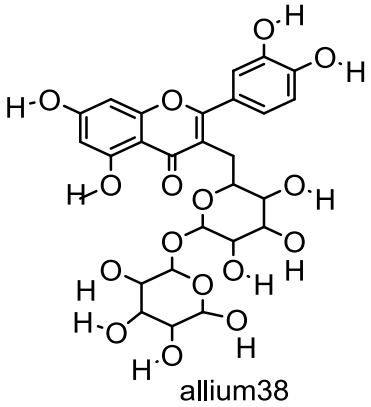


Glaziovianin-A



Xanthotoxin

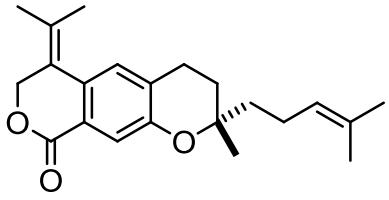
Rao et al [Rao *et al.* 2012] studied the protein-ligand interaction of 267 compounds obtained from different parts of the plants Allium sativum, Coriandrum sativum, Dacus carota, Murrayyakoneigii, Eucalyptus, Calendula officinalis and Lycopersicon esculentum with aldose reductase as the target protein. Molecular docking and re-scoring of top ten compounds (using GOLD, Auto Dock Vina, eHiTS, Patch Dock and MEDock) followed by rank-sum technique identified compound allium **38** to be the best inhibitor for the target enzyme.



allium38

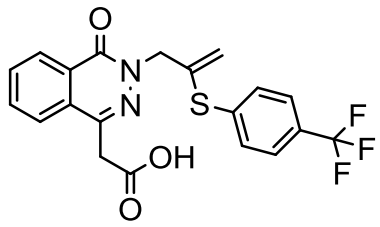
Akhila, S *et al.* [Akhila *et al.* 2012] carried out the docking studies of different constituents of Helicteres isora a known antidiabetic plant. Auto dock 4.0 was used for the studies and the receptors chosen were aldose reductase and insulin receptor protein. Analysis of the results showed that, with both the receptors, best results were obtained with yohimbine with the best binding energy and probably it attributes most to

the found activity. Similarly Manju et al [Manju *et al.* 2012] screened the different constituents of traditionally used drug *Peperomia pellucida*, by in-silico approach for diabetes to determine the active constituents attributing to its anti diabetic activity. Autodock 4.0 software was used for the docking on aldose reductase. Once again Yohimbine was found to be the bioactive constituent responsible for the observed antidaibetic activity and it was found to be more potent that the standard quercetin.

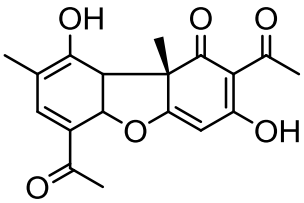


Peperomia pellucid

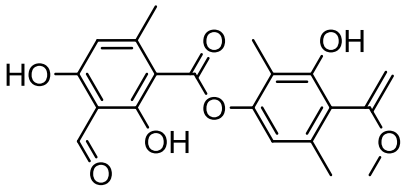
In another study Raghu *et al.* [Raghu *et al.* 2014] investigated the aldose reductase inhibition potential of edible lichen *Parmotrema tinctorum* (Nyle) Hale. The kinetic studies of different extracts i.e. ethyl acetate extract (PTEAE) and ethanol (PTEE) of *P. tinctorum* follow different mechanism. PTEAE was found to be competitive inhibitor while PTEE was a mixed inhibitor. The major constituents present in *P. tinctorum* was docked on protein aldose reductase and the results that the constituent usnic acid exhibits maximum binding potential with binding energy of -8.9 kcal/mol. The inhibition constant (Ki), was found to be 300.42 nM for usnic acid which is closer to the inhibition constant of the standard zopolrestat of 26.0 nM. The docking studies with atranorin, salazinic acid and usnic acid show that they have an interaction with Leu301 which is a nonpolar residue and it is conserved in the active site of both human and rat. Obtained results indicate that usnic acid, atranorin, and salazinic acid bind in a competitive fashion to aldose reductase.



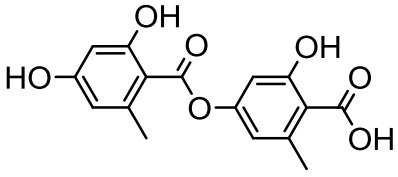
Zopolrestat



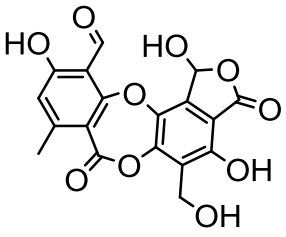
Usnic acid



Atranorin

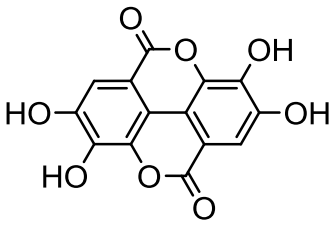


Lecanoric acid



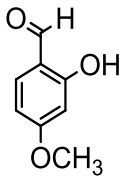
Salazinic acid

Similarly, Sabina *et al*. [Sabina *et al.* 2014] carried out docking studies on 15 active components of herbal preparation Triphala against aldose reductase to understand its binding and interaction pattern and also to deduce the most active principle responsible for the antidiabetic activity. Patch Dock online server was used for the experiments and the resulting ligand complexes were studied using PyMol viewer. The active ingredients such as pelagic acid, chebulinic acid, sennoside, ellagitannin, casuarinin and vitamin C showed remarkable interactions and hence affinity for aldose reductase. Among them, ellagitannin was found to be the most potent inhibitor with 18 hydrogen bonds with AR.

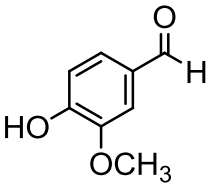


Ellagitannin

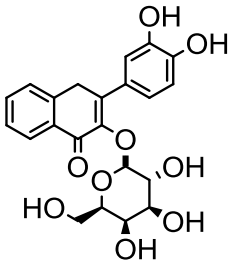
In another study, Vijayan *et al.* [Vijayan *et al.* 2016] evaluated the inhibitory effects of dietary spices on aldose reductase. The authors selected several phytochemicals from Curcuma longa (turmeric) Zingiber officinale (ginger), Trigonella foenum graecum (fenugreek), and Allium sativum (garlic) and carried out docking for lead identification. Further, to understand the dynamic behavior, molecular dynamics simulations were performed for the protein ligand interactions. High docking score, sustained protein ligand interactions and binding affinity were observed for Gingerenones A, B and C, quercetin, lariciresinol and calebin A found in the selected spices. The docking scores improved at the end of MD simulations for these protein- ligand interactions compared to the initial ones obtained. Also, they displayed better docking results, ADMET properties and interactions compared to the most potent aldose reductase inhibitors such as sorbinil, epalrestat and ranirestat. Simillarly, Raju *et al.* [Raju.*et al.* 2016] selected the medicinal plant *Hemidesmus indicu* and its known 41 metabolites were subjected to docking studies. The active components Vanillin, 2- hydroxy-4-methoxy benzaldehyde, Isoquercetin, Hyperoside, Phenylpropanoid and p-methoxysalicylic aldehyde exhibited best affinity for AR.



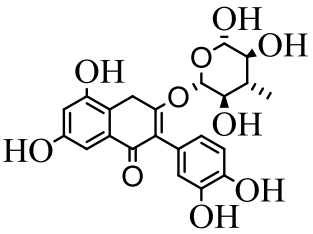
2- Hydroxy 4- methoxy benzaldehyde



Vannillin



Hyperoside



Isoqurectin

CONCLUSION

The present review reveals that a variety of structures exhibit potent aldose reductase inhibitory activity. Most of the active constituents of the medicinal plants evaluated exhibit potent aldose reductase activity and this is noteworthy as most of the synthetic ALRs failed at the clinical trials due to toxicity related problems. In this context, constituents of edible spices and known medicinal plants in use should facilitate development of safe and effective aldose reductase inhibitors. A fraction of these compounds have been shown to be active in vivo on animal models and they are under clinical trials to treat the abnormalities associated with diabetes. The binding site and protein flexibility studies should facilitate design and synthesis of new and safe aldose reductase inhibitors of therapeutic significance and hence counter long term complications associated with diabetes.

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Correspondence Author:
Sayyed Hussain Sajjansab
Sir Sayyed College of Arts, Commerce and Science, Roshangate, Aurangabad, India

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