Indian Journal of Science and Technology Vol. 3 No. 8 (Oct 2010) ISSN: 0974- 6846

Molecular docking study of bark-derived components of *Cinnamomum cassia* on aldose reductase

K. Sivakumari[1], A. Flora Mary Cyril Rathinabai[1], P.K. Kaleena[1], P. Jayaprakash[1] and R. Srikanth[2]
[1]*Dept. of Zoology, Presidency College, Chennai-600005, India*
[2]*Dept. of Biotechnology, Sri Venkateswara College of Engineering, Chennai-602105, India*
dr.sivakumari@rediffmail.com

Abstract

Aldose reductase (AR) is an enzyme associated with retinopathy of both type 1 and type 2 diabetic patients. AR is inhibited by giving chemical drugs to prevent diabetic retinopathy, but is associated with deleterious side effects. Compounds isolated from plants are safer than chemical drugs and have a lot of potential. In the present study, three components *viz*., cinnamaldehyde, cinnamic acid and cinnamyl alcohol derived from the bark of *Cinnamomum cassia* were used to evaluate their efficiency in inhibiting AR activity. For this, the AR protein structure database was downloaded from PDB and its pictorial database was downloaded from PDBsum. Structural visualization of AR was done by RasMol. Using Q-SiteFinder, prediction of ligand binding site was done. The three dimensional structures of inhibitors *viz*., cinnamaldehyde, cinnamic acid and cinnamyl alcohol were downloaded from ChemSketch. Docking studies were carried out using ArgusLab software. Docking studies of cinnamaldehyde, cinnamic acid and cinnamyl alcohol against AR was undertaken to gain insight into the binding mode of the investigated compounds at the active site of AR. All compounds were found to be active against AR as indicated by docking results; the best being cinnamaldehyde. Results suggest that cinnamaldehyde, cinnamic acid and cinnamyl alcohol should be evaluated further for therapeutic use in combination with other diabetic drugs. Further, this may be confirmed by drug trials in animal models to find out the optimum dose and its efficiency in inhibiting AR activity to treat diabetic related complications.

Keywords: Diabetes, aldose reductase, cinnamon, molecular docking.

Introduction

Diabetic retinopathy is one of the most important complications in both type 1 and type 2 diabetes. Supportive evidence for a genetic role for retinopathy derives from twin, family and transracial studies demonstrating the importance of inherited factors in the etiology of diabetes and its complications (Pyke & Tattersall, 1973, DCCTRG, 1993; Alcolado, 1998). Over the past several years, progress has been made in identifying some of the genes associated with diabetic retinopathy. Candidate genes have been identified for diabetic retinopathy by family linkage studies and case control studies by Radha *et al*. (2002). The possible candidate genes contributing to the development of diabetic retinopathy are genes for aldose reductase (AR), nitric oxide synthase (NOS), receptor for advanced glycation end products (RAGE), angiotensin converting enzyme (ACE), human leucocyte antigen (HLA) and vascular endothelial growth factors (VEGF).

The other names of aldose reductase gene are aldo-keto reductase family 1, member b1; akr1b1. The alternative titles or symbols for the gene are aldose reductase; ar, aldehyde reductase 1; aldr1 and its gene map locus is 7q35. Human ALR2 gene, the gene encoding aldose reductase has been localized to chromosome 7q35 and consists of 10 exons extending over 18 kb of DNA (Nishamura et al., 1994).There is growing evidence to implicate ALR2 in the pathogenesis of diabetic microvascular disease. Aldose reductase (AR; EC 1.1.1.21) is also present in the lens, retina, schwann cells of peripheral nerves, placenta and red blood cells. The abnormal expression and activity of this enzyme seem to play an important role in diabetic complications. Several studies have pointed out that a high level of AR in the erythrocyte of both type 1 and type 2 diabetic patients is associated with the presence of retinopathy (Graham, 1991a, b; Hamada et al., 1991, 1993). AR has been implicated in the pathogenesis of various diabetic complications (Yabe-Nishimura, 1998). The enzyme catalyzes the reduction of various aldehydes, including the aldehyde form of glucose, using NADPH as a cofactor. AR converts glucose to sorbitol, which is next converted to fructose by sorbitol dehydrogenase (SDH) using the cofactor NAD^+. This is the so-called polyol pathway, an alternate route of glucose metabolism. Under hyperglycemic conditions, acceleration of the polyol pathway leads to accumulation of sorbitol and osmotic disturbances in the lens (Nagata *et al*., 1989). Fructose produced by the enhanced flux through the pathway promotes non-enzymatic glycation (Tsukushi *et al*., 1999). It is also proposed that the polyol pathway may elicit a decreased NAD^+/NADH ratio, the condition illustrated as pseudohypoxia as opined by Williamson *et al*. (1993), Trueblood and Ramasamy (1998) and Nakamura *et al*. (2001). Such metabolic perturbation is postulated to provoke early tissue damage in the ocular lens, retina, peripheral nerve and the renal glomerulus, where insulin-independent uptake of glucose takes place.

Fig.1 depicts the polyol pathway as described by Brownlee (2001) and Sheetz and King (2002). The polyol

Indian Journal of Science and Technology Vol. 3 No. 8 (Oct 2010) ISSN: 0974- 6846

pathway reduces toxic aldehydes generated by ROS to inactive alcohols. AR, *via*. the consumption of NADPH, is responsible for the initial and rate-limiting step in the process. Glucose can be reduced to sorbitol and eventually fructose, through this pathway, but AR has a low affinity for glucose at normal concentrations. Elevated intracellular glucose can increase AR activity, resulting in significantly decreased NADPH. NADPH is also required for glutathione reductase (GR) activity, which reduces glutathione (GSH) – a major mechanism for reducing intracellular oxidative stress (Lee & Chung, 1999). Decreased NADPH and resulting decreased GR activity ultimately increases oxidative stress and activates pathways that increase cellular damage. According to Brownlee (2001), AR reduces aldehydes generated by ROS to inactive alcohols and glucose is converted to sorbitol, using NADPH as a co-factor. For cells in which AR activity is sufficient to deplete reduced GSH, oxidative stress is augmented. Sorbitol dehydrogenase (SDH) oxidizes sorbitol to fructose using NAD^+ as a co-factor.

During hyperglycemia, reduction of glucose to sorbitol by AR constitutes the first and the rate-limiting step of the polyol pathway that converts glucose to fructose *via*., SDH. In this pathway both NADPH and NAD^+ are consumed as cofactors for the enzymes AR and SDH. Osmotic stress due to accumulation of sorbitol and oxidative stress due to changes in the ratio of $NADPH/NADP^+$ and reduced NAD (NADH)/NAD^+ are the major cause of various complications of secondary diabetes. Fig. 2 depicts the role of polyol pathway in diabetic complications.

Aldose reductase inhibitors

AR is a target enzyme for the treatment of diabetic complications. Owing to the limited number of currently available drugs for the treatment of diabetic complications, the discovery of new inhibitors of AR that can potentially be optimized as drugs appears highly desirable. Aldose reductase inhibition (ARI) is ostensibly an ideal target for reducing the deleterious effects associated with polyol pathway activation. Due to its proposed involvement in the development of diabetic complications, AR has been a drug target in the clinical management of secondary complications of diabetes including cataract (Tomlinson *et al.,* 1994). Previously studied inhibitors of AR were largely from two chemical classes, spirosuccinamide/hydantoins and carboxylic acids. Each class has its own drawbacks regarding selectivity, *in vivo* potency and human safety. As a result, the pathogenic role of AR in diabetic retinopathy remains controversial. ARI-809 is a recently discovered AR inhibitor (ARI) of a new structural class, pyridazinones, which has high selectivity for aldose Vs AR. Chemical drugs such as sorbinil, tolrestat or lidorestat, ponalrestat, zopolrestat, zenarestat, epalrestat, fidarestat, ranirestat, statil, alrestatin and ALO1576 are some of the well-studied inhibitors that have also been clinically tested. However, to date, none of the currently available synthetic ARIs have proved clinically effective and some have in fact had deleterious side effects. Many AR inhibitors that have been developed as drug candidates virtually have failed although some are commercially available in several countries. Therefore, evaluating natural sources for ARI potential may lead to the development of safer and more effective agents against diabetic complications.

Plants constitute a rich source of bioactive chemicals against aldose reductase (Kador, *et al.,* 1985; Haraguchi *et al.,* 1996a; Yoshikawa *et al.,* 1998; Matsuda *et al.,* 1999; Kim, *et al.,* 2001; Lee, 2002a; Lee *et al.,* 2005). Since many of them are largely free from adverse effects and have excellent pharmacological actions, they could lead to the development of new classes of possibly safer anti-diabetic agents. Additionally, some flavonoids and polyphenols as well as sugar derivatives are found to be effective inhibitors of AR (Kador, *et al.,* 1985; Haraguchi *et al.,* 1996b; Yoshikawa *et al.,* 1998; Matsuda *et al.,* 1999; Kim, *et al.,* 2001; Lee *et al.,* 2005). Therefore, much effort has been focused on the plants for potentially useful products as commercial ARIs or as lead compounds. The importance of finding effective ARIs led scientists to further investigate these natural compounds.

Structurally distinct compounds such as flavonoids, benzopyrans, spirohydantoins, alkaloids, nonsteroidal anti-inflammatory agents and quinones have all been shown to inhibit the enzyme with various degrees of efficacy and specificity as stated by Raskin and Rosenstock (1987) and Bhatnagar and Srivastava (1992). Moreover there is an increased interest in recent times to identify many natural (plant/spice) sources for their therapeutic properties, mainly because most of the plant and plant products (including natural spices) are largely free from adverse effects and are being used as a source of diet and traditional medicine. One such plant source is *Cinnamomum cassia*, commonly known as the cinnamon.

C. cassia Blume (Chinese cinnamon) is the dried bark of cassia which is a small, bushy, ever green tree, 18-20 m high and 40-60 cm diameter with a straight and cylindrical trunk and grey brown bark, 13-15 mm thick when mature. It comes under the family *Lauraceae*. Its barks and leaves are commercial parts. Dried cassia bark is the spice. The essential oil is called cassia cinnamon oil (*Oleum cinnamon*). Apart from its use as spice, it is a well known medicine reinforcing '*yang*', the body fire. '*Gui zhi*' (dried twig of cinnamon) is collected in spring and summer and dried in the sun or in the shade used in decoctions, has analgesic and anti-pyretic properties. This plant species, the commercial source of cinnamon, is not only important as a spice, but in East Asia is considered to have some medicinal properties, *e.g*., as a stomachic agent, an antimicrobial agent, an astringent and a carminative agent as pointed out by Namba (1986), Lee and Ahn (1998) and Kim *et al.* (2000). It is rich in essential oils and tannins as stated by Morimoto *et al*. (1986).

The inhibition of AR by cinnamaldehyde, cinnamic acid and cinnamyl alcohol from *Cinnamomum cassia* had

Indian Journal of Science and Technology Vol. 3 No. 8 (Oct 2010) ISSN: 0974- 6846

Fig. 1. Aldose reductase & the polyol pathway.

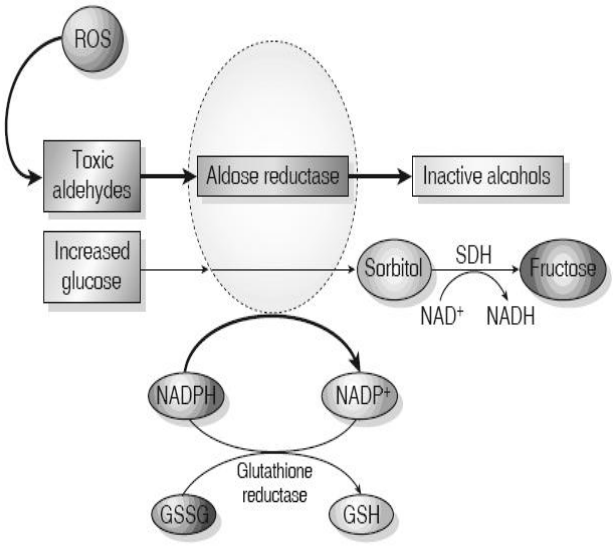


Fig. 2. Involvement of polyol pathway in diabetic complications.

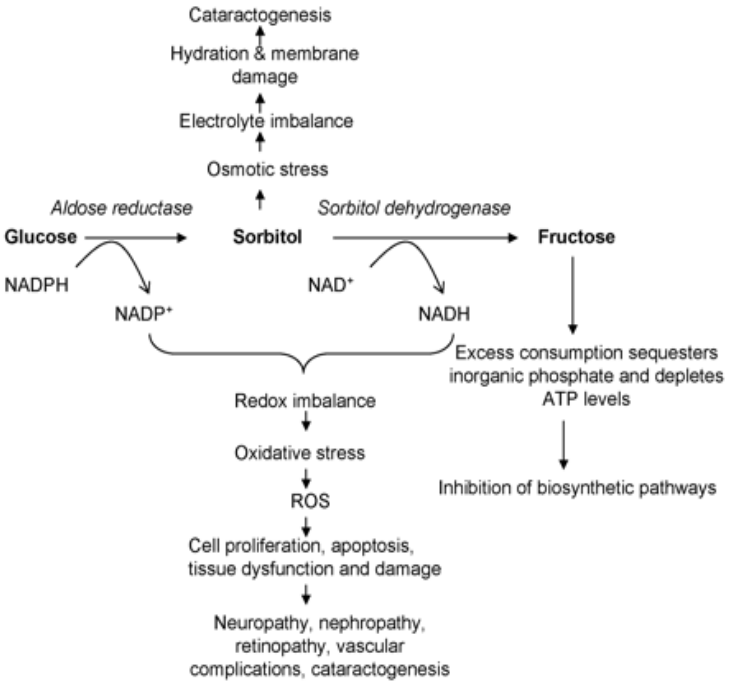


Fig. 4. Three-dimensional structures of AR

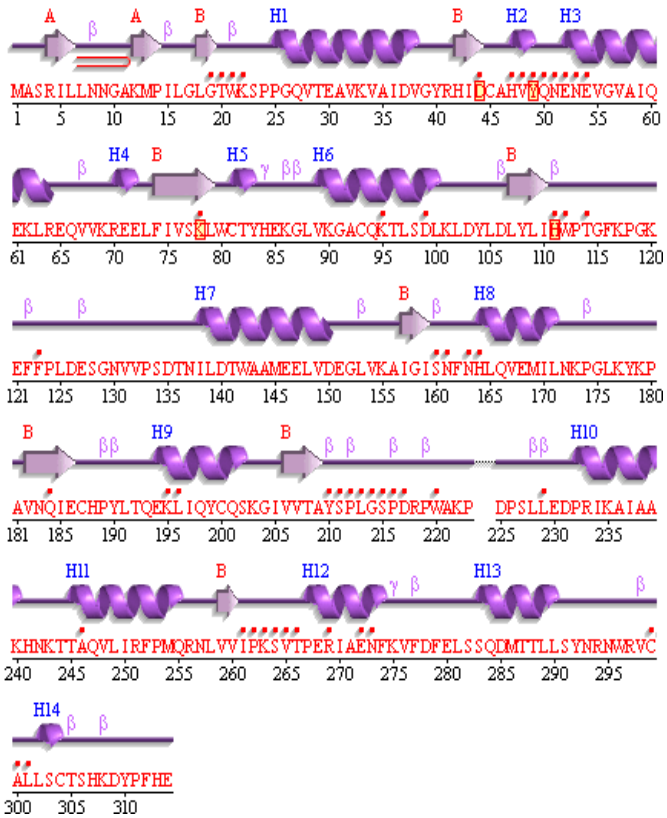
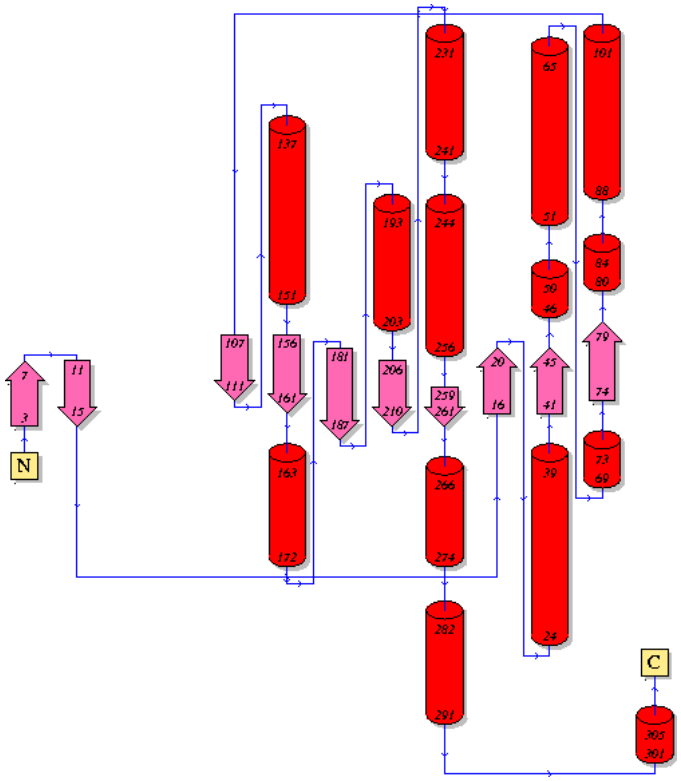


Fig. 3.Topology & amino acid residues of AR.



Indian Journal of Science and Technology Vol. 3 No. 8 (Oct 2010) ISSN: 0974- 6846

been evaluated by Lee (2002a), where the active components from the extract of *C. cassia* were isolated by bioassay-guided separation. Cinnamaldehyde was approved with a conditional acceptable daily intake for man (ADI) of 1.25 mg/kg by FDA/WHO (FAO/WHO Report, 1968). Furthermore, the oral LD_{50} of cinnamaldehyde for rat and mice varies from 3.4 g/kg to greater than 5.0 g/kg (Opdyke, 1978). Many investigations have shown that cinnamaldehyde has antibacterial (Moleyar & Narasimham, 1992), antibotulinal (Bowles & Miller, 1993) and intestinal modulating effects (Lee & Ahn, 1998). However, relatively little work has been done on AR inhibitory activity of *C. cassia* despite its excellent pharmacological action in East Asia (Morimoto *et al*., 1986; Lee, 2002a). ARI isolated from *C. cassia* bark may be a good source for medicinal foodstuffs and lead compounds as alternatives for ARIs currently used.

Results indicate that *C. cassia* bark-derived materials have an inhibitory effect *in vitro* against rat lens AR. Based upon the limited data and some earlier findings, cinnamaldehyde may be useful as a lead compound for an anti-diabetic agent and a medicinal foodstuff, although *in vivo* efficacy and clinical utility remain to be evaluated. In order to explore the inhibitory mechanism of cinnamon towards AR, bioinformatics plays a major role, where docking can be done using computer software to find out the binding sites and docking mechanisms. This provides a clear view on how the drug acts upon AR and inhibits its activity. According to Rohs *et al*. (2005), the dynamics of biological processes depend on the structure and flexibility of the interacting molecules. In particular, the conformational diversity of DNA allows for large deformations upon binding. Drug-DNA interactions are of high pharmaceutical interest since the mode of action of anticancer, antiviral, antibacterial and other drugs is directly associated with their binding to DNA. A reliable prediction of drug-DNA binding at the atomic level by molecular docking methods provides the basis for the design of new drug compounds. Scientists evaluated the role of several proteins that are likely to be involved in diabetic retinopathy by employing multiple sequence alignment using ClustalW tool and constructed a phylogram tree using functional protein sequences extracted from NCBI. Phylogram was constructed using Neighbor-Joining Algorithm in bioinformatics approach. It was observed that AR is closely associated with diabetic retinopathy. It is likely that vascular endothelial growth factor, pro-inflammatory cytokines, advanced glycation end products and adhesion molecules that also play a role in diabetic retinopathy may do so by modulating the activity of AR. The results imply that methods designed to normalize AR activity could be of significant benefit in the prevention and treatment of diabetic retinopathy (Rao *et al.,* 2008). In view of the above, it was felt that molecular docking of AR activity inhibition by using the bark-derived components of *C. cassia* as such as cinnamaldehyde, cinnamic acid and cinnamyl alcohol would be helpful to understand the underlying mechanism. This study would provide a clear understanding on the mode of action of the above mentioned bark-derived components of *C. cassia* against AR and can be used as an AR inhibitory drug to reduce diabetic related complications.

Materials and methods

I. Structure retrieval

a. The protein data bank (PDB): The structure homologues for AR protein sequence query was retrieved in PDB.

b. The research collaboratory for structural bioinformatics (RCSB): The molecular shape of AR was retrieved from RCSB PDB (PDB – www.rcsb.org/).

c. PDBsum: The PDBsum (PDBsum-www.ebi.ac.uk/pdbsum/), a pictorial database that provides an at-a-glance overview of the contents of each 3D structure deposited in the Protein Data Bank (PDB) was used to get the 3-D structure of AR.

II. Structure visualization-RASMOL: RasMol (RasMol-www.rasmol.org/), a molecular graphics program intended for the visualization of proteins, nucleic acids and small molecules was used for structural visualization of AR.

III. Prediction of binding site-Q-SiteFinder: Q-SiteFinder (Q-siteFinder-www.bioinformatics.leeds.ac.uk/qsitefinder/), a new method of ligand binding site prediction was used. Both Q-SiteFinder and Pocket-Finder allow us to upload a PDB file or select one from the Protein Database. The proteins were initially scanned for ligands and potential ligands were identified.

IV. Three dimensional structure of inhibitors-CHEMSKETCH: The Chemical structure of Cinnamaldehyde, Cinnamic acid and Cinnamyl alcohol was drawn using ChemSketch (ChemSketch – www.acdlabs.com/download/), a quite powerful chemical structure drawing program.

V. Docking: Docking was done with the ARGUSLAB software (ArgusLab-www.arguslab.com/), in which the result is being obtained on the basis of pose energy. Docking calculations attempt to place '*Ligands into Binding Sites*'. Before docking a molecule, first it is needed to define the atoms that make up the *Ligand* like drug, inhibitor*, etc*., and the *Binding Site* on the protein where the drug binds. The final results are based on the type of calculation we run such as Geometry optimization-search for 'Final Geometry' and Electronic spectra-search for 'Excited state properties'.

Results and discussion

The AR protein of human was retrieved and analyzed and it was docked to ARI compounds namely, cinnamaldehyde, cinnamic acid and cinnamyl alcohol from *C. cassia*. The results are presented as follow:

Indian Journal of Science and Technology Vol. 3 No. 8 (Oct 2010) ISSN: 0974- 6846

Fig. 5a. Ball & stick model of AR in RASMOL

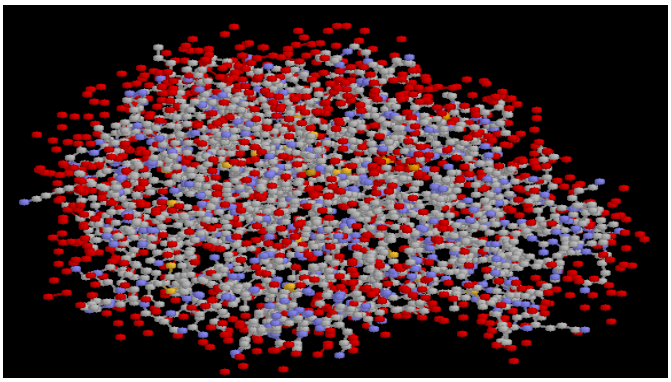


Fig. 5b. Cartoon model of AR showing secondary structures in RASMOL

Fig. 5c. Wireframe model of AR in RASMOL

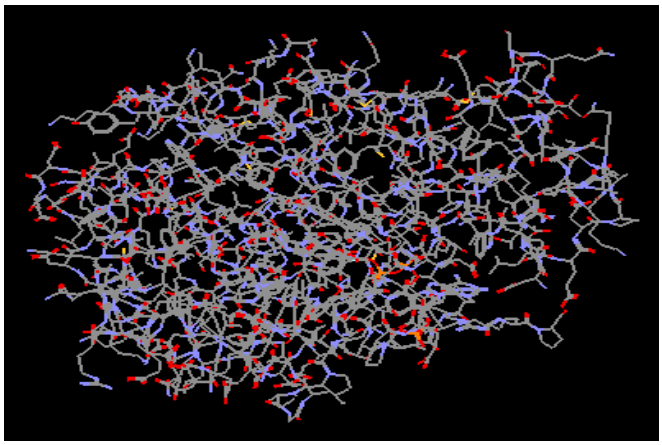
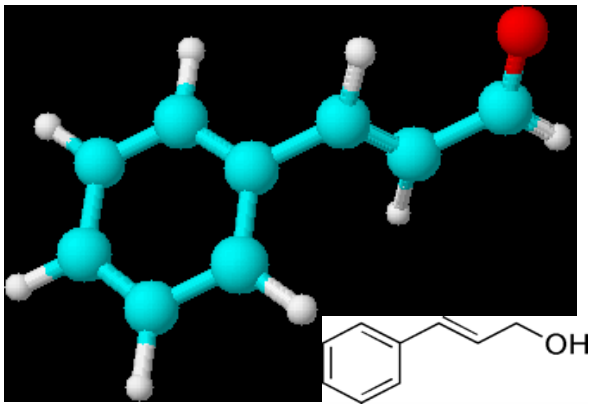


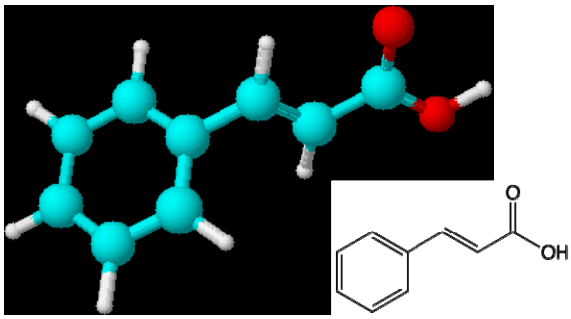
Fig. 6. Structure of cinnamaldehyde obtained from ChemSketch in ball & stick model.



Properties of cinnamaldehyde obtained from ChemSketch

Molecular formula	= C_9H_8O
Formula weight	= 132.15922
Composition	= C (81.79%) H (6.10%) O (12.11%)
Molar refractivity	= 42.32 ± 0.3 cm^3
Molar volume	= 127.7 ± 3.0 cm^3
Parachor	= 319.1 ± 4.0 cm^3
Index of refraction	= 1.577 ± 0.02
Surface tension	= 38.9 ± 3.0 dyne/cm
Density	= 1.034 ± 0.06 g/cm^3
Dielectric constant	= Not available
Polarizability	= 16.78 ± 0.5 $10^{-24}cm^3$
Monoisotopic mass	= 132.057515 Da
Nominal mass	= 132 Da
Average mass	= 132.162445 Da

Fig.7. Structure of cinnamic acid obtained from ChemSketch in ball & stick model



Properties of cinnamic acid obtained from ChemSketch.

Molecular formula	= $C_9H_8O_2$
Formula weight	= 148.15862
Composition	= C (72.96%) H (5.44%) O (21.60%)
Molar refractivity	= 43.70 ± 0.3 cm^3
Molar volume	= 125.0 ± 3.0 cm^3
Parachor	= 332.0 ± 4.0 cm^3
Index of refraction	= 1.616 ± 0.02
Surface tension	= 49.7 ± 3.0 dyne/cm
Density	= 1.184 ± 0.06 g/cm^3
Dielectric constant	= Not available
Polarizability	= 17.32 ± 0.5 $10^{-24}cm^3$
Monoisotopic mass	= 148.052429 Da
Nominal Mass	= 148 Da
Average Mass	= 148.161749 Da

Indian Journal of Science and Technology Vol. 3 No. 8 (Oct 2010) ISSN: 0974- 6846

I. Retrieving three dimensional structure of human aldose reductase

The structure of AR with PDB Id: 2I16 (Petrova *et al.,* 2006) was taken for further analysis. This structure was analyzed to know details of the AR molecule. The secondary structure information about AR protein has been retrieved from PDBsum database. The topology of the different secondary structures of AR and the aminoacid residues in which each helices and sheets are formed are given in Fig. 3. The three-dimensional structures of AR are composed of similar α/β TIM-barrels (Fig. 4). The structure folds into α/β-barrel with a core of 8 parallel β-strands. Adjacent strands are connected by 8 parallel α-helical segments running anti-parallel to the β-sheet. The symmetry of the TIM-barrel is disrupted by the presence of two short anti-parallel β-strands at the N-terminus connected by a tight turn closing the bottom of the barrel (El-Kabbani *et al*., 1998). The PDB file was downloaded and viewed in RasMol and their various models are given in Fig.5a, b, c.

II. Binding site prediction – Q-SiteFinder

The protein structure of AR was given as input to Q-SiteFinder tool and binding site of the protein was predicted. Ten best '*binding sites*' were predicted. The amino acids and the atoms involved in the site were listed.

III. Drawing three dimensional structures of inhibitors-CHEMSKETCH

The chemical structure of the following ARIs collected from literatures were drawn in ChemSketch and converted in to three dimensional structures and are given in Fig. 6, 7 and 8.

IV. Docking *ArgusLab:* Using ArgusLab, the receptor, AR pdb file and the ligand pdb file were taken and the protein side chain molecules were removed with the help of various tool controls for their perfect visualization. Hetero atoms were removed and the molecule was used for docking. The binding site molecules were stored as separate PDB file and that was used for the analysis. Then, the protein file and the ligand pdb file were loaded and docking studies were performed. The best docked conformation with its binding energy was found and details are given below. The binding site used was the site 1 predicted by Q-SiteFinder. While performing docking the protein and ligand appeared in a grid as shown below and the various binding configurations are analyzed and finally the list of best poses are given as output and saved as ArgusLab.agl files. The details are given in Fig. 9a, b, c.

Best score for docking:

Cinnamaldehyde: Binding energy for docking : -8.04 kcal/mol

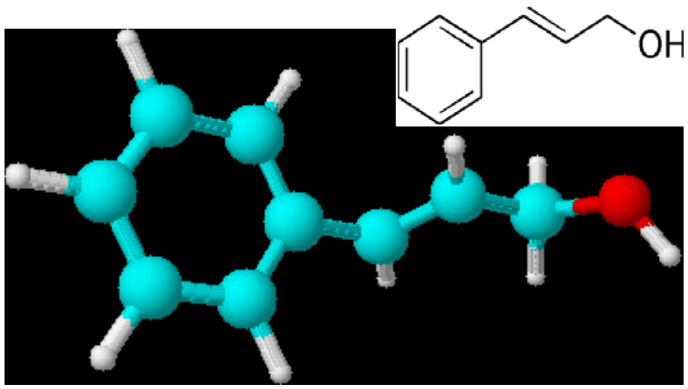
Cinnamic acid: Binding energy for docking : -8.88 kcal/mol

Cinnamyl alcohol: Binding energy for docking : -8.88 kcal/mol

The ARIs effectively docked in to the binding site of AR protein indicating that they are efficient drug compounds. All these inhibitors *viz*., cinnamaldehyde, cinnamic acid, cinnamyl alcohol showed efficient docking as indicated by binding energy and all are efficient inhibitors. This fact is supported by the findings of Lee (2002a). It has been well acknowledged that plant-derived extracts and phytochemicals are potential alternatives to synthetic inhibitors against AR (Kador, *et al.,* 1985; Haraguchi *et al.,* 1996b; Yoshikawa *et al.,* 1998; Matsuda *et al.,* 1999; Kim, *et al.,* 2001, Lee, 2002a; Lee *et al.,* 2005). Currently, the compounds isolated from plants known to inhibit AR are flavonoids and flavonoid-related compounds. These include 5, 7, 4'-trihydroxy-3, 6-dimethoxyflavone from *Acanthospermum australe* (Shimizu *et al.,* 1987), myricetin 3-O-(4'-acetyl)-fucoside from *Anthocepharus chinensis* (Haraguchi *et al.,* 1998) and dihydroflavonol rhamnosides and quercetin 3-rhamnoside from *Engelhardtia chrysolepis* (Haraguchi *et al.,* 1996b).

In a study, the active component isolated from *C. cassia* bark against AR was identified as *trans*-cinnamaldehyde, a low molecular weight cinnamic acid analogue. It has been reported by Namba (1986), Lee and Ahn (1998) and Kim *et al.* (2000) that the *C. cassia* bark-derived materials including cinnamaldehyde, cinnamic acid, cinnamyl alcohol and eugenol have

Fig. 8. Structure of Cinnamyl alcohol obtained from ChemSketch in Ball and Stick model.



Properties of Cinnamyl alcohol

Molecular Formula	= $C_9H_{10}O$
Formula Weight	= 134.1751
Composition	= C (80.56%) H (7.51%) O (11.92%)
Molar Refractivity	= 43.67 ± 0.3 cm^3
Molar Volume	= 127.9 ± 3.0 cm^3
Parachor	= 326.9 ± 4.0 cm^3
Index of Refraction	= 1.598 ± 0.02
Surface Tension	= 42.6 ± 3.0 dyne/cm
Density	= 1.048 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 17.31 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 134.073165 Da
Nominal Mass	= 134 Da
Average Mass	= 134.178397 Da

Indian Journal of Science and Technology Vol. 3 No. 8 (Oct 2010) ISSN: 0974- 6846

antibacterial, astringent, carminative and stomachic effects. In the study carried out by Lee (2002a), the inhibitory activities of cinnamaldehyde, cinnamic acid, cinnamyl alcohol and eugenol against AR. Inhibitory responses varied with the chemicals tested. At 0.5 mg/mL, Cinnamaldehyde completely inhibited (100%) AR. On the otherhand, the inhibitory activities of cinnamic acid, cinnamyl alcohol and eugenol were 63, 41 and 48%, respectively. These results indicate that the inhibitory activity of *C. cassia* extract against AR is primarily caused by cinnamaldehyde. The IC_{50} values of cinnamaldehyde, cinnamic acid, cinnamyl alcohol and eugenol were determined to be 0.003, 0.38, >0.5 and >0.5 mg/mL, respectively.

Lee (2002a) suggested that cinnamaldehyde isolated from *C. cassia* barks may be useful as a lead compound and a medicinal foodstuff for AR inhibition. In the present study also, docking of AR by cinamaldehyde showed efficient docking than the other two *viz*., cinnamic acid, cinnamyl alcohol. Anyhow all the three components have more or less similar docking energies and so all the three compounds can be used for inhibiting AR activity. It might be expected that the active components isolated from the bark of *C. cassia viz*., cinnamaldehyde, cinnamic acid, cinnamyl alcohol would have some pharmacological actions against *Diabetes mellitus*. Further this may be confirmed by drug trials in animal models to find out the optimum dose and its efficiency in inhibiting AR activity and reduce diabetic related complications.

Fig. 9a. Docking of AR with cinnamaldehyde.

Fig. 9b. Docking of AR with cinnamic acid.

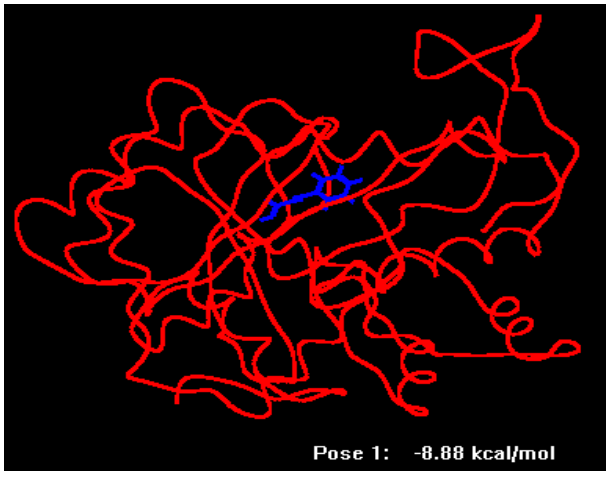
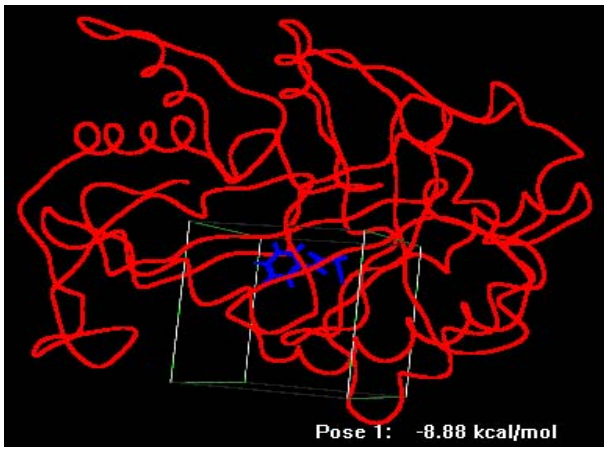


Fig. 9c. Docking of AR with cinnamyl alcohol.



References

1. Alcolado J (1998) Genetics of diabetic complications. *Lancet*. 351, 230-231.
2. Bhatnagar A and Srivastava SK (1992) Aldose reductase: congenial and injurious profiles of an enigmatic enzyme. *Biochem. Med. Metab. Biol.* 48, 91-121.
3. Bowles BL and Miller AJ (1993) Antibotulinal properties of selected aromatic and aliphatic aldehydes. *J. Food Prot.* 56, 788-794.
4. Brownlee M (2001) Biochemistry and molecular cell biology of diabetic complications. *Nature.* 414, 813-820.
5. DCCTRG (The diabetes control and complications trial research group) (1993) The effect of intensive insulin treatment of diabetes on the development and progression of long term complications in insulin dependent *Diabetes mellitus*. *N. Engl. J. Med.* 329, 977-986.
6. FAO/WHO (1968) Specifications for the identity and purity of food additives and their toxicological evaluation: some flavoring substances and non-nutritive sweetening agents. 11th report of the joint FAO/WHO expert committee on food additives, FAO nutrition meetings report series no. 44, *Wld. Hlth Org. Techn. Rep. Ser. No*. 383.
7. Graham A, Brown L, Hedge PJ, Gammack AJ and Markham AF (1991a) Structure of the human aldose reductase gene. *J. Biol. Chem.* 266, 6872-6877.
8. Graham A, Heath P, Morten JEN and Markham AF (1991b) The human aldose reductase gene maps to chromosome region 7q35. *Hum. Genet.* 86, 509-514.
9. Hamada Y, Kitoh R and Raskin P (1991) Increased erythrocyte aldose reductase activity in type 1 diabetic patients. *Diabetic Med.* 8, 226-231.
10. Hamada Y, Kitoh R and Raskin P (1993) Association of erythrocyte aldose reductase activity with diabetic complications in type 1 *Diabetes mellitus*. *Diabetic Med.* 10, 33-38.
11. Haraguchi H, Ohmi I, Sakai S and Fukuda A (1996a) Effect of *Polygonum hydropiper* sulfated flavonoids on

Indian Journal of Science and Technology Vol. 3 No. 8 (Oct 2010) ISSN: 0974- 6846

lens aldose reductase and related enzymes. *J. Nat. Prod.* 59, 443-445.
12. Haraguchi H, Ohmi I, Masuda H, Tamura Y, Mizutani K, Tanka O and Chou WH (1996b) Inhibition of aldose reductase by dihydroflavonols in *Engelhardtia chrysolepis* and effects on other enzymes. *Experientia* 52, 564-567.
13. Haraguchi H, Kanada M, Fukuda A, Naruse K, Okamura N and Yagi A (1998) An inhibitor of aldose reductase and sorbitol accumulation from *Anthocepharus chinensis. Planta Medica* 64, 68-69.
14. Kador PF, Robison WG and Kinoshita JH (1985) The pharmacology of aldose reductase inhibitors. *Ann. Rev. Pharmacol. Toxicol.* 25, 691-714.
15. Kim MK, Kim SY and Lee HS (2001) Rat lens aldose reductase inhibitory activities of oriental medicinal plants. *Agric. Chem. Biotechnol.* 45, 84-88.
16. Kim MK, Lee SE and Lee HS (2000) Growth-inhibiting effects of Brazilian and oriental medicinal plants on human intestinal bacteria. *Agric. Chem. Biotechnol.* 43, 54-58.
17. Lee AY and Chung SS (1999) Contributions of polyol pathway to oxidative stress in diabetic cataract. *FASEB J.* 1, 23-30.
18. Lee HS and Ahn YJ (1998) Growth-inhibiting effects of *Cinnamomum cassia* bark-derived materials on human intestinal bacteria. *J. Agric. Food. Chem.* 46, 8-12.
19. Lee HS (2002a) Inhibitory activity of *Cinnamomum cassia* bark-derived component against rat lens aldose reductase. *J. Pharm. Pharmaceut. Sci.* 5(3), 226-230.
20. Lee YS, Lee S, Lee HS, Kim BK, Ohuchi K and Shin KH (2005) Inhibitory effects of isorhamnetin-3-Q-beta-D-glucoside from *Salicornia herbacea* on rat lens aldose reductase and sorbitol accumulation in streptozotocin-induced diabetic rat tissues. *Biol.Pharm.Bull.*28(5),916-918
21. Matsuda H, Murakami T, Yashiro K, Yamahara J and Yoshikawa M (1999) Antidiabetic principles of natural medicines. Aldose reductase and glucosidase inhibitors from the roots of *Salacia oblonga* Wall. (Celastraceae): Structure of a new friedelane-type triterpene, kotalagenin 16-acetate. *Chem. Pharm. Bull.* 47, 1725-1729.
22. Moleyar V and Narasimham P (1992) Antibacterial activity of essential oil components. *Int. J. Food Microbiol.* 16, 337-342.
23. Morimoto S, Nonaka G and Nishioka I (1986) Tannins and related compounds XXXVIII. Isolation and characterization of flavan-3-ol glucosides and procyanidin oligomers from cassia bark (*Cinnamomum cassia* Blume). *Chem. Pharm. Bull.* 34, 633-642.
24. Nagata M, Hohman TC, Nishimura C, Drea CM, Oliver C and Robison WG Jr (1989) Polyol and vacuole formation in cultured canine lens epithelial cells. *Exp. Eye Res.* 48, 667-677.
25. Nakamura J, Kasuya Y, Hamada Y, Nakashima E, Naruse K, Yasuda Y, Kato K and Hotta N (2001) Glucose-induced hyperproliferation of cultured rat aortic smooth muscle cells through polyol pathway hyperactivity. *Diabetologia* 44(4), 480-487.
26. Namba T (1986) Colored Illustrations of Wakan-Yaku In: *The Crude Drugs in Japan, China and the Neighbouring Countries*. Hoikusha Publishing, Osaka, Japan.
27. Nishimura C, Saito T, Ito T, Omori Y and Tamimoto T (1994) High levels of erythrocyte aldose reductase and diabetic retinopathy in NIDDM patients. *Diabetologia* 37, 328-330.
28. Opdyke DLJ (1978) Fragrance raw materials monographs. *Food Cosmet. Toxicol.* 16, 687-689.
29. Pyke DA and Tattersall RB (1973) Diabetic retinopathy in identical twins. *Diabetes* 22, 613-618.
30. Radha V, Rema M and Mohan V (2002) Genes and diabetic retinopathy. *Indian J. Ophthalmol.* 50(1), 5-11.
31. Rao AA, Thota H, Gumpeny RS, Akula A, Changalasetty SB, Challa SR, Ravavarapu T, Akula SP, Divakar CH, Srinivas K and Das UN (2008) Bioinformatics analysis of diabetic retinopathy using functional protein sequences. *Med. Hypotheses* 70(1), 148-155.
32. Raskin P and Rosenstock J (1987) Aldose reductase inhibitors and diabetic complications. *Am. J. Med.* 83, 298-306.
33. Sheetz MJ and King GL (2002) Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA* 288, 2579-2588.
34. Shimizu M, Horie S, Arisawa M, Hayashi T, Suzuki S, Yoshizaki M, Kawasaki M, Terashima S, Tsuji H, Wada S, Ueno H, Morita N, Berganza LH, Ferro E and Basualdo I (1987) Chemical and pharmaceutical studies on medicinal plants in Paraguay. I. Isolation and identification of lens aldose reductase inhibitor from 'Tapecue' *Acanthospermum australe* O.K. *Chem. Pharm. Bull.* 35, 1234-1237.
35. Tomlinson DR, Stevens EJ and Diemel LT (1994) Aldose reductase inhibitors and their potential for the treatment of diabetic complications. *Trends Pharmacol.Sci.* 15,293-297.
36. Trueblood N and Ramasamy R (1998) Aldose reductase inhibition improves altered glucose metabolism of isolated diabetic rat hearts. *Am. J. Physiol.* 275, H75-H83.
37. Tsukushi S, Katsuzaki T, Aoyama I, Takayama F, Miyazaki T, Shimokata K and Niwa T (1999) Increased erythrocyte 3-DG and AGEs in diabetic hemodialysis patients: Role of the polyol pathway. *Kidney Int.* 55, 1970-1976.
38. Williamson J, Kilo C and Tilton RG (1992) Mechanism of glucose- and diabetes-induced vascular dysfunction. In: *Hyperglycemia, Diabetes, and Vascular Disease* (eds. Ruderman N, Williamson J and Brownlee M) pp. 107-132. American Physiological Society, New York, USA.
39. Williamson JR, Chang K, Frangos M, Hasan KS, Ido Y, Kawamura T, Nyengaard JR, van den Enden M, Kilo C and Tilton RG (1993) Hyperglycemic pseudohypoxia and diabetic complications. *Diabetes* 42(6), 801-813.
40. Yabe-Nishimura C (1998) Aldose reductase in glucose toxicity: A potential target for the prevention of diabetic complications. *Pharmacol. Rev.* 50, 21-33.
41. Yoshikawa M, Shimada H, Norihisa N, Li Y, Toguchida I, Yamahara J and Matsuda H (1998) Antidiabetic principles of natural medicines. II. Aldose reductase and a-glucosidase inhibitors from Brazilian natural medicine, the leaves of *Myrcia multiflora* DC. (Myrtaceae): Structures of myrciacitrins I and II and Myrciaphenones A and B. *Chem. Pharm. Bull.* 46, 113-119.