Journal of Applied Pharmaceutical Science Vol. 3 (01), pp. 013-020, January, 2013
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2013.30104
ISSN 2231-3354

Docking Studies of Chlorogenic Acid against Aldose Redutcase by using Molgro Virtual Docker Software

Sadaf Naeem[1], Peter Hylands[2] and David Barlow[2]
[1]Biophysics Unit, Department of Biochemistry, University of Karachi, Karachi-75270, Pakistan
[2]Institute of Pharmaceutical Science, Franklin-Wilkin Building, King's College London, 150 Stamford Street, London SE1 9NH, United Kingdom.

ARTICLE INFO

Article history:
Received on: 17/09/2012
Revised on: 30/10/2012
Accepted on: 05/12/2012
Available online: 28/01/2013

Key words:
Chlorogenic acid,
aldose reductase,
MVD,
Diabetes.

ABSTRACT

Docking studies of chlorogenic acid against aldose reductase, an enzyme involved in diabetic complications, have been performed, in order to evaluate the inhibitory effects of chlorogenic acid on this enzyme. The docking studies were performed using Molgro Virtual Docker (MVD) software. From the several available alternative methods to incorporate protein flexibility in docking studies, the use of multiple crystal structures with different bound ligands was applied here, thus, of the available crystal structures of the non- mutated aldose reductase enzyme from *Homo sapiens*, five were selected for the final docking studies. The docking results of chlorogenic acid with selected aldose reductase crystal structures shows that it forms hydrogen bonds with at least two out of three key active site residues (Tyr48, His110 and Trp111). It also form hydrogen bonds to other active site residues, in particular Thr113. The average MolDock score and the MolDock Re-rank score for cholorogenic acid are -119.34 Kcal/mol and -114.92 Kcal/mol respectively. The docking results show that chlorogenic acid fits well in the active site of aldose reductase and interact with the residues in the active site which are crucial for their biological activity, thus, it could a potent inhibitor of aldose reductase enzyme and thus be used for prevention/treatment of diabetic complications.

INTRODUCTION

Chlorogenic acid (5-O-caffeoylquinic acid), a phenolic compound found ubiquitously in plants, is an antioxidant and metal chelator (Kono *et al*., 1998). It has been reported that the intake of this compound in diabetic rats, lowered glucose concentration (Andrade-Cetto and Wiedenfeld, 2001; Rodriguez de Sotillo and Hadley, 2002) and the intake of *Cecropia obtusifolia* leaf extracts, that are rich in chlorogenic acid, resulted in a significant reduction in plasma glucose concentrations in persons with type 2 diabetes (Herrera-Arellano *et al*., 2004). Although, various preventive effects of cholorogenic acid on diabetes were reported but the effects of this compound on diabetic complications are still unknown. Therefore, the effect of chlorogenic acid on aldose reductase, an enzyme involved in diabetic complications such as retinopathy (Reddy *et al*., 2008, Van den Enden *et al*., 1995), nephropathy (Sato *et al*., 1992, Dunlop *et al*., 2000), neuropathy (Oates *et al*., 1997), cataract formation (Lee *et al*. 1995) or angiopathy (Jay *et al*., 2006) has been studies here.

* *Corresponding Author*
Email: sadafnaeem_4@yahoo.com
Mobile: +92-(0)331-2071530

Aldose reductase (EC 1.1.1.21, AR), first and the rate limiting enzyme of the polyol pathway converts glucose to sorbitol, in the presence of NADPH as reducing cofactor. The second enzyme of the pathway, sorbitol dehydrogenase (EC 1.1.1.14), oxidizes sorbitol to fructose with NAD as cofactor (Yabe-Nishimura *et al.*, 1998; Brownlee *et al*., 2001). Various studies have showed that the patho-physiological activity of aldose reductase (AR) plays a key role in the development of diabetic complications (Yabe-Nishimura *et al*., 1998; Kador *et al*., 1988; Tomlinson *et al*., 1994; King *et al*., 1996). So, a possible strategy to prevent the onset and progression of the diabetic complications is to inhibit this enzyme (Miyomoto *et al*., 2002; Costantino *et al*., 2000; Srivastava *et al.*, 2005; Costantino *et al.*, 1999). Several crystal structures of aldose reductase have been solved by X-ray diffraction complexed with NADPH (Figure 1) and diverse aldose reductase inhibitors (ARIs). All these crystal structures have shown that the active site of this enzyme is a large, deep, ellipsoidal cavity, approximately 4 Å x 15Å wide and 15 Å deep, wherein the nicotinamide ring of the NADPH cofactor and the substrate-binding site are found. The binding site is divided into 2 sub-pockets (Figure 2): an anion binding site and a specificity pocket.

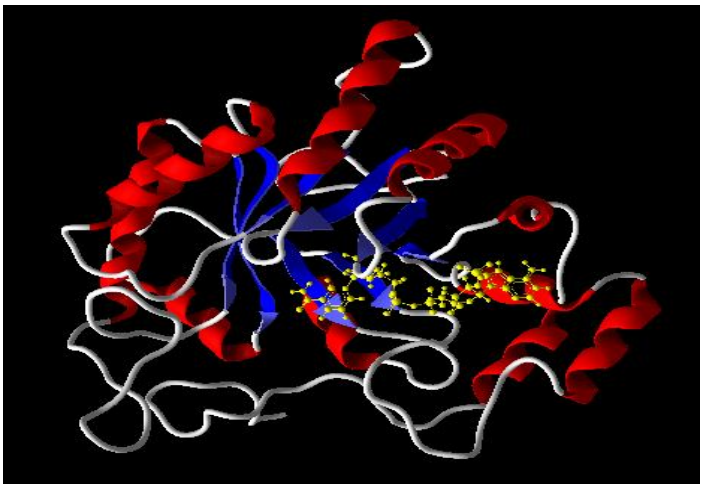


Fig. 1: Structural cartoon of aldose redutase (PDB code 1ADS; Wilson, 1992) [The α helices and β strands are represented as coils (red) and arrows (blue), respectively. NADPH is represented in ball and stick (yellow). Model prepared using MolDock (Thomsen, 2006)].

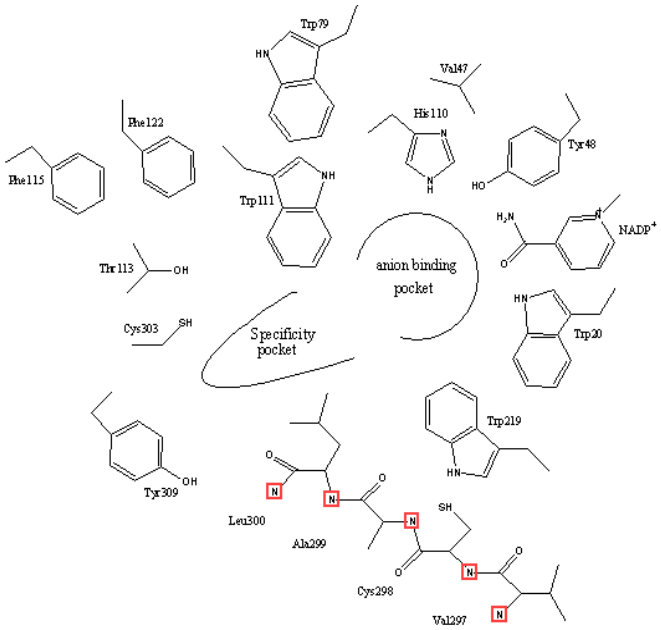


Fig. 2: A schematic diagram showing the ligand binding site of aldose reductase (Adapted from Sotriffer, 2004).

The anion binding pocket is formed by hydrophilic residues (Tyr48, His110, Trp111) and the 4-*pro*-R-hydrogen of the nicotinamide ring of NADPH and involved in catalysis, whereas, the second, specificity pocket is formed by hydrophobic residues Trp111, Trp20, Trp79, Ala299, Leu300 and Phe122. (Yabe-Nishimura *et al.*, 1998; El-Kabbani *et al.*, 1997**,** Nakano *et al.*, 1996). It can adopt various conformations depending on the size and properties of the bound ligand and is responsible for the various substrate and inhibitor specificities. (Harrison *et al.*, 1997). Hydrogen bonds are formed between the polar groups of the inhibitor and the active-site residues Tyr48, His110, and Trp111 AR (Wilson *et al.*, 1993; Urzhumtsev *et al.*, 1997; Harrison *et al.*, 1997; Rogniaux *et al.*, 1999; Oka *et al.*, 2000).

Thus, the inhibitor binding site is a positively charged anion well formed by Tyr48, His110 and the nicotinamide ring (Harrison *et al.*, 1997; Harrison *et al.*, 1994) and the required structural elements of aldose reductase inhibitors are proposed as an aromatic ring system to form hydrophobic or π-π stacking interactions with the hydrophobic amino acid residues in the active site (Tyr20) and an acidic ionisable group such as those of carboxylic acids and spirohydantoin which can anchor to the anionic binding site ($Asp43^{-}$/$Lys77^{+}$/$Tyr48^{+}$/$NADP^{+}$complex (Miyamoto *et al.*, 2002a; Lee *et al.*, 1998; Sun *et al.*, 2003).

During this study, cholrogenic acid have been docked into the active site of aldose resductase by using the Molgro Virtual Docker (MVD) software. Docking methods typically use an energy-based scoring function to identify the most energetically favorable conformation of a ligand when bound to the macromolecular target. Lower energy scores indicates more favored protein-ligand complexes. Molecular docking is thus an optimization problem, where the task is to find the ligand binding mode with lowest potential energy. The process of docking involves sampling the coordinate space of the target binding site and scoring each possible ligand pose within that site, the highest scoring pose then taken as the predicted binding mode for that compound. There are many different docking programs now available and they differ in the nature of the sampling algorithms they employ, in their manner of handling ligand and protein flexibility, in the scoring functions they use, and in the cpu time they required. Some of the most widely used docking programs include: Gold (Jones *et al*., 1995, 1997), Dock (Ewing *et al.*, 2001), FlexX (Rarey, *et al.*, 1996; Kramer *et al.*, 1999), Glide (Halgren *et al.*, 2004; Friesner *et al.*, 2004), Fred (McGann *et al.*, 2003), LigandFit (Venkatachalam *et al.*, 2003), Slide (Schnecke *et al*., 2000) , AutoDock (Morris *et al.*, 1998), ICM (Abagyan *et al*., 1994), QXP (McMartin *et al.*, 1997), Surflex (Jain, 2003) and MVD (Thomsen *et al*., 2006).

Each of these programs attempts to predict the most likely structures of protein-ligand complexes and then to quantify the free energy of ligand binding, at the same time keeping the computing time within acceptable limits to allow for a rapid docking of large chemical libraries. In the studies reported here, MVD was used, because it showed higher docking accuracy when benchmarked against other available docking programs (MD: 87%, Glide:82%, Surflex:75%, FlexX:58%) (Thomsen *et al.*, 2006) and has been shown to be successful in several recent studies (Pripp, 2007; Sapre *et al.*, 2008; Chauhan *et al.*, 2009; Paul *et al.*, 2010), but also for reasons of cost and user-friendliness. In most docking studies, the target proteins are assumed to be rigid objects. This major assumption (neglecting protein flexibility) can cause errors (Carlson *et al*., 2000) and lead to inaccurate binding pose (Cavasotto *et al*., 2004; Osterberg *et al.*, 2002; Murray *et al.*, 1999). Proteins are flexible and dynamic objects and using a single protein conformation ignores important dynamic aspects of protein ligand binding (Jorgensen *et al*., 1991). Dealing with protein flexibility is one of the major challenges in the development of docking methods (Klebe *et al*., 2006; Sousa *et al*., 2006; Teague *et al*., 2003) - because of the high

dimensionality of the search space involved and because of the complexity of energy function to be computed. Thus, a number of attempts have been made to introduce protein flexibility into docking protocols (Carlson *et al*., 2002; Klebe *et al*., 2006; Guvench *et al.*, 2009), among which the use of multiple protein crystal structures is considered the best option to take advantage of the full flexibility of the receptor (Carlson *et al*., 2000).

MATERIAL AND METHODS

In this study, docking of cholorogenic acid against AR have been performed using MVD software. Usually, a single rigid crystal structure of an enzyme is used for docking studies, but here in order to incorporate the protein flexibility in this docking studies, five different crystal structures of AR, were selected (Table 1), from the available 95 crystal structures of AR (June 2009) held in the Protein Databank (PDB) (Deshpande 2005) accessed at the URL: (http://www.rcsb.org/pdb), - under the criteria that they had a reasonable resolution (≤ 2.8 Å) and involved the *non-mutated* aldose reductase enzyme from *Homo sapiens*, in complex with different ligands.

Chlorogenic acid have been docked against each of these five selected AR crystal structures and 10 independent runs were performed with the guided differential evolution algorithm, with each of these docking runs returning one solution (pose). The MolDock scoring function used by MVD is derived from the PLP scoring functions originally proposed by Gehlhaar *et al*. (1995, 1998) and extended later by Yang *et al*. (2004).

The 10 solutions obtained from the 10 independent docking runs were re-ranked, in order to further increase the docking accuracy, by using a more complex scoring function. In MVD, along with the docking scoring function terms, a Lennard Jones 12-6 potential (Morris, 1998) and sp^2-sp^2 torsion terms were also used. On the basis of pilot docking studies, the MolDock re-rank scores were selected for ranking the inhibitor poses, and for all the aldose reductase docking performed here, the poses selected as the best were taken as those with the highest MolDock re-rank score. Aldose reductase crystal structures were directly downloaded to the workspace of MVD from the PDB (Deshpande, 2005) accessed at the URL: (http://www.rcsb.org/pdb). The structure of chlorogenic acid has been drawn on ChemDraw software and imported to the MVD workspace in 'sdf' format. In order to make accurate predictions, it is important that the imported structures have been properly prepared, that is, the atom connectivity and bond orders are correct and partial atomic charges are assigned. PDB files often have poor or missing assignment of explicit hydrogens, and the PDB file format cannot accommodate bond order information. All necessary valency checks and H atom addition were thus performed using the utilities provided in MVD. The binding site specifies the region of interest where the docking procedure will look for promising poses (ligand conformations). MolDock automatically identifies potential binding sites (also referred as cavities or active sites) by using its cavity detection algorithm. The cavities within a 30 x 30 x 30 $Å^3$ cube centered at the experimentally known ligand position were used. The cavities that are identified by the cavity detection algorithm are then used by the guided differential evolution search algorithm to focus the search, to that specific area during the docking simulation. In the case of the crystal structures for aldose reductase complexes, the program generally identified five different binding sites (Figure 3). From these five predicted cavities the one with the highest volume (205.13 $Å^3$) was selected for consideration, as it includes the bound ligand.

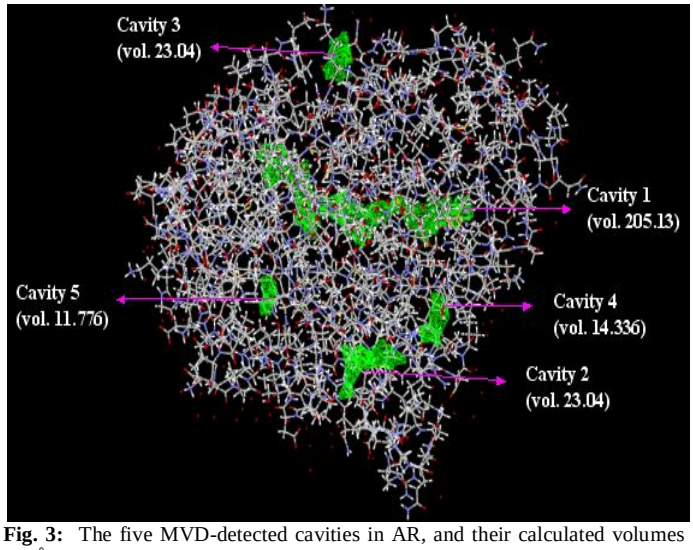


Fig. 3: The five MVD-detected cavities in AR, and their calculated volumes (in Å) (PDB code: 1T40 (Ruiz, 2004); detected cavities: green; carbon atoms: grey; oxygen atoms: red; nitrogen atoms: blue)

The number of runs specifies the number of times that the docking simulation is repeated for each ligand chosen to be docked. By default MVD sets the number of docking runs '*n*' as 10. Pilot docking studies were first conducted with *n* = 10, 50 and 100, to determine if the increase in number of runs yielded improvements in docking scores/success, but no improvements in docking results were observed with the increase in *n*, so all the studies reported here used *n* = 10.

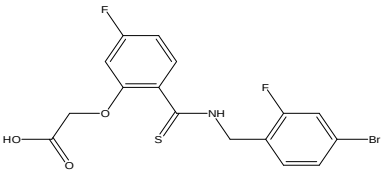
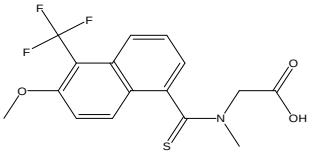
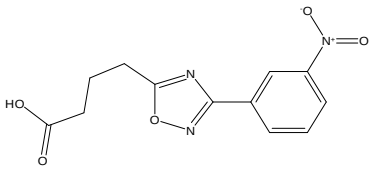
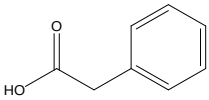
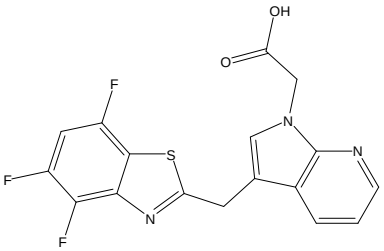
For each AR docking, each pose was inspected individually and the interaction of the ligand with the amino acids in the binding site viewed.

RESULTS AND DISCUSSION

The most convenient way to incorporate protein flexibility in the docking process is to perform docking using an ensemble of static receptor conformations and nowadays, this approach is applied more and more in virtual screening experiments (Bowman *et al*., 2007b; Cheng *et al*., 2008).

It is this approach that was applied here, using a collection of selected AR crystal structures with different bound ligands to provide different conformations of the protein and allow for structural changes in the protein upon ligand binding (Subramanian *et al.*, 2006). Thus, five of the aldose reductase crystal structures bound to different ligands— 2FZD, IUS0, 3G5E, 2INE and 2IKG were used in this study (Table 1).

Table. 1: List of crystal structures of aldose reductase used for docking studies (PDB ID = four character PDB identifier representing each entry).

PDB ID	Ligand	Ligand structure	Ligand volume (Å)	Reference
1US0	IDD594		921.8	Howard, 2004
2FZD	Tolrestat		860.2	Steuber, 2006
2IKG	Nitrophenyl oxadiazole type inhibitor		729	Steuber, 2007
2INE	Phenylacetic acid		480.8	Brownlee, 2006
3G5E	IDD740		898.2	Van Zandt, 2009

(Kinoshita *et al.,* 2002; Steuber *et al.,* 2007; Steuber *et al*., 2006; Van Zandt *et al.,* 2009; Howard *et al.,* 2004.

Chlorogenic acid was docked with all of these five selected human crystal structures of AR bound to different ligands. In each docking run, the best poses were selected on the basis of their MVD re-rank scores and the mean of the 5 re-rank scores was then computed as the final score for each compound.

The MVD score and the re-rank scores of the best poses for each of the docking studies of chlorogenic acid with five crystal structures of AR, and their average is presented in Table 2. The average MolDock score and the MolDock Re-rank score obtained for cholorogenic acid are -119.34 Kcal/mol and -114.92 Kcal/mol respectively. The best docking poses obtained on the basis of MVD re-rank score for chlorogenic acid with each of the 5 crystal structures of aldose reductase are presented in Figures 4. The reported crystallographic studies have shown that the interactions of ligands in the catalytic site of AR are mostly polar (Howard *et al.,* 2004), and in most of the AR crystal structures involving the more potent inhibition, these compounds are all carboxylic acids, with their carboxylate groups firmly anchored in the active site, with hydrogen bonds to His110, Tyr48, and Trp111

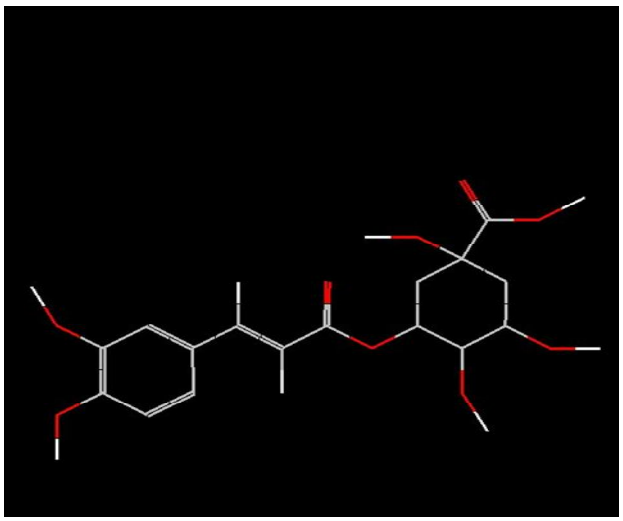
Chlorogenic acid (Figure 4a) is formed by the esterification of caffeic acid and quinic acids. While docking of chlorogenic acid with the five crystal structures of aldose reductase, it is oriented in the active site such that it forms hydrogen bond with at least two of the three key residues i.e. Tyr48, His110 and Trp111.

Table. 2: MVD and Re-rank score (kcal/mol) for chlorogenic acid when docked with five aldose reductase crystal structures.

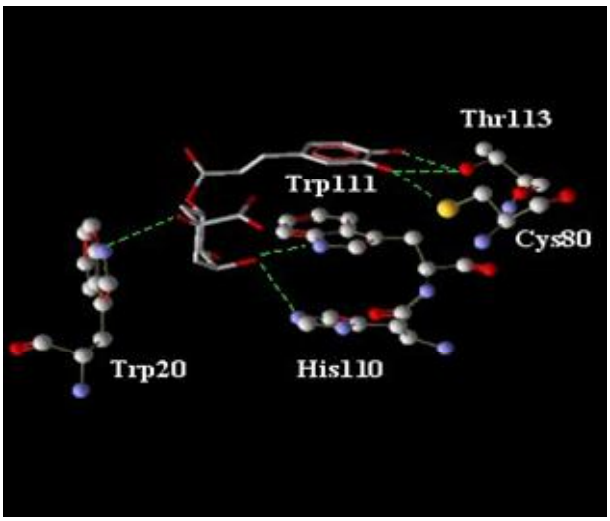
	MolDock Score	MolDock Rerank Score
2FZD	-107.75	-101.48
2IKG	-92.35	-91.368
2INE	-122.83	-119.73
3G5E	-132.78	-127.71
IUS0	-140.99	-134.32
Average Score	-119.34 ± 19.5	-114.92 ± 18

Along with these three residues hydrogen bonds are also formed with some other active site amino acids among which Cys298 and Thr113 are most frequent.

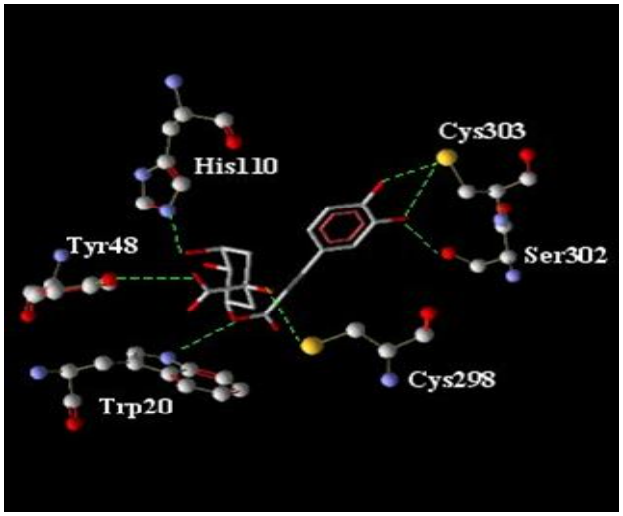
The comparison of the binding of Tolrestat in the active site of aldose reductase (PDB ID: 2FZD) (Figure 5a) and docking of cholorogenic acid in the active site of the same enzyme (Figure 5b) clearly shows similarity in the binding of the two compounds.



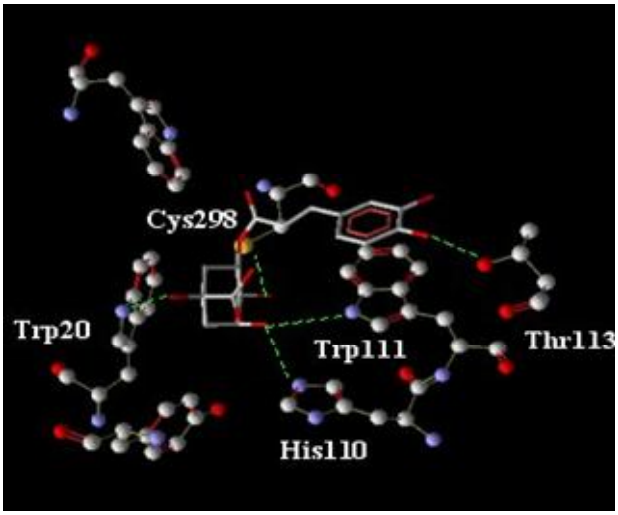
A-chiorogenicacid



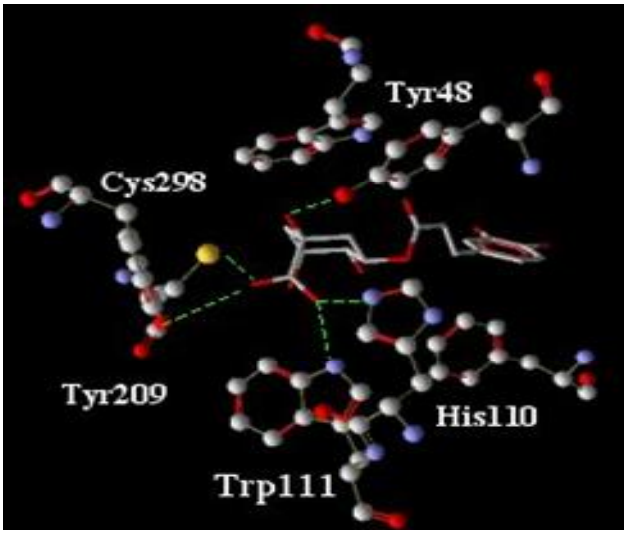
B- 1USO



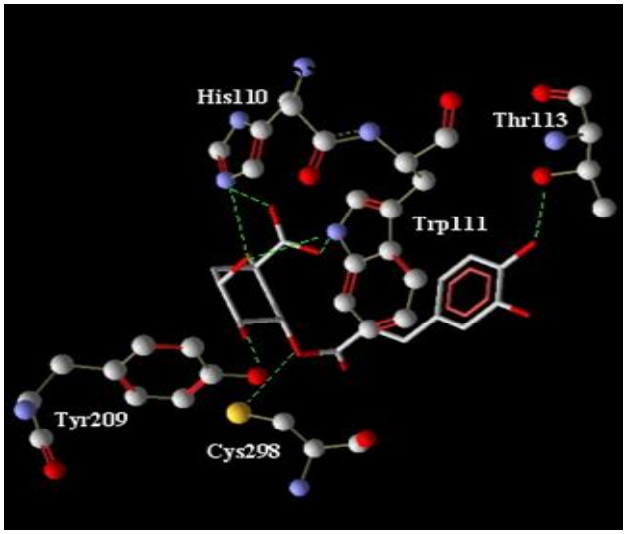
C-2FZD



D-2IKG



E-2INL



F-3GSE

Fig. 4: The best scored docking solution of Chlorogenic acid (a) with the five selected crystal structures of AR (b to f). (The coenzyme NADPH is removed for the sake of clarity. Amino acids in the active site are presented in ball and stick with element colour and ligand is presented in thick lines with element colour (where carbon is grey, oxygen is red, nitrogen is blue and sulphur is yellow and hydrogen in white). Green lines represent the hydrogen bonds in between the ligand and the active site of AR).

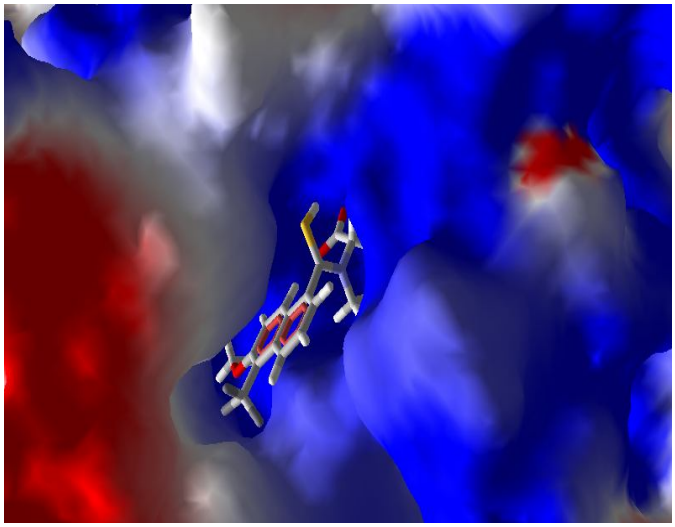


Fig. 5a: Binding of Tolrestat in the active site of aldose redustase (PDB ID 2FZD)[The anion binding pocket is at top right (blue) and specificity pocket is at bottom left (red)].

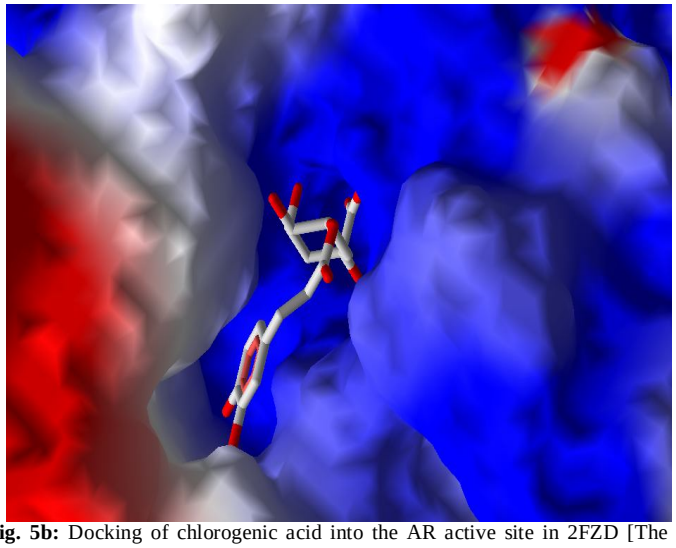


Fig. 5b: Docking of chlorogenic acid into the AR active site in 2FZD [The anion binding pocket is at top right (blue) and specificity pocket is at bottom left (red)].

CONCLUSION

The docking studies detailed above provide estimates of the inhibitory activities of the docked ligand. The results show that chlorogenic acid fits well in the active site of aldose reductase and also interact with the residues in the active site which are important for their biological activity, thus, chlorogenic acid could be a putative inhibitor of aldose reductase and can be used to prevent the onset/treatment of diabetic complications.

REFERENCES

Andrade-Cetto A., Wiedenfeld H. Hypoglycemic effect of Cecropia obtusifolia on streptozotocin diabetic rats. J. Ethnopharmacol. 2001; 78: 145-149.

Barril X., Morley S.D. Unveiling the full potential of flexible receptor docking using multiple crystallographic structures. J. Med. Chem. 2005; 48: 4432-4443.

Bowman A.L., Nikolovska-Coleska Z., Zhong H., Wang S., Carlson H.A. Small molecule inhibitors of the MDM2–p53 interaction discovered by ensemble-based receptor models. J. Am. Chem. Soc. 2007b; 129: 12809-12814.

Brownlee J.M., Carlson E., Milne A.C., Pape E., Harrison D.H.T. Structural and thermodynamic studies of simple aldose reductase–inhibitor complexes. Bioorganic Chemistry 2006; 34: 424-444.

Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001; 414: 813-820.

Carlson H.A. Protein flexibility and drug design: how to hit a moving target. Curr. Opin. Chem. Biol. 2002; 6: 447-452.

Carlson H.A., Masukawa K.M., Rubins K., Bushman F.D., Jorgensen W.L., Lins R.D., Briggs J.M., McCammon J.A. Developing a dynamic pharmacophore model for HIV-1 integrase. J. Med. Chem. 2000; 43: 2100-2114.

Cavasotto C.N., Abagyan R.A. Protein flexibility in ligand docking and virtual screening to protein kinases. J. Mol. Biol. 2004; 337: 209-225.

Chauhan P., Shakya, M. Model based design of inhibitors for c-jun. Bioinformation 2009**;** 4: 223-228.

Cheng L.S., Amaro R.E, Xu D., Li W.W., Arzberger P.W., McCammon J.A. Ensemble-based virtual screening reveals potential novel antiviral compounds for avian influenza neuraminidase. J. Med. Chem. 2008; 51: 3878-3894.

Costantino L., Rastelli G., Gamberini M.C., Barlocco D. Pharmacological approaches to the treatment of diabetic complications. Expert Opin. Ther. Patents. 2000; 10: 1245-1262.

Deshpande N., Addess K.J., Bluhm W.F., Merino-Ott J.C., Townsend-Merino W., Zhang O., Knezevich C., Xie, L. Li Chen, Feng Z., Green R.K., Flippen-Anderson J.L., Westbrook J., Berman H.M., Bourne P.E. The RCSB Protein Data Bank: a redesigned query system and relational database based on the mmCIF schema. Nucleic Acids Research 2005, 33: Database issue D233–D237

Dunlop M. Aldose reductase and the role of the polyol pathway in diabetic nephropathy. Kidney International. 2000;77: S3-S12.

El-Kabbani O., Carper D.A., McGowan M.H., Devedjiev Y., Rees-milton K.J., Flynn T.G. Studies on the inhibitor binding site of porcine aldehyde redctase: Crystal structure of the holoenzyme-inhibitor ternary complex. Proteins. 1997; 29: 186-192.

Ewing T.J., Makino S., Skillman A.G. Kuntz I.D. DOCK 4.0: Search strategies for automated molecular docking of flexible molecule databases. J. Comput. Aided Mol. Design. 2001; 15: 411-428.

Gehlhaar D.K., Bouzida D., Rejto P.A. Fully automated and rapid flexible docking of inhibitors covalently bound to serine proteases. Proceedings of the Seventh International Conference on Evolutionary Programming 1998; 449-461.

Gehlhaar D.K., Verkhivker G., Rejto P.A., Fogel D.B., Fogel L. J., Freer S. T. Docking conformationally flexible small molecules into a protein binding site through evolutionary programming. Proceedings of the Fourth International Conference on Evolutionary Programming 1995; 615-627

Guvench O., MacKerell A.D. Jr. Computational evaluation of protein-small molecule binding. Curr. Opin. Struct. Biol. 2009; 19: 56-61.

Halgren T.A., Murphy R.B., Friesner R.A., Beard H.S., Frye L.L., Pollard, W.T., Banks J.L. Glide: a new approach for rapid, accurate docking and scoring. 2. Enrichment factors in database screening. J. Med. Chem. 2004 47: 1750-1759.

Harrison D.H., Bohren K.M., Petsko G.A., Ringe D., Gabbay K.H. The alrestatin double decker: Binding of two inhibitor molecules to human aldose reductase reveals a new specificity determinant. Biochemistry. 1997; 36: 16134-16140.

Harrison D.H., Bohren K.M., Ringe D., Petsko G.A., Gabbay K.H. An anion binding site in human aldose reductase: Mechanistic implications for the binding of citrate, cacodylate, and glucose 6-phosphate. Biochemistry. 1994; 33: 2011-2020.

Herrera-Arellano A., Aguilar-Santamaría L., García-Hernández B., Nicasio-Torres P., Tortoriello J. Clinical trial of Cecropia obtusifolia

and Marrubium vulgare leaf extracts on blood glucose and serum lipids in type 2 diabetics. Phytomedicine. 2004; 11: 561-566.

Howard E.I., Sanishvili R., Cachau R.E., Mitschler A., Chevrier B., Barth P., Lamour V., Van Zandt M., Sibley E., Bon C., Moras D., Schneider T.R., Joachimiak A., Podjarny A. Ultrahigh resolution drug design I: Details of interactions in human aldose reductase – inhibitor complex at 0.66**.** PROTEINS: Struct. Funct. Bioinformat. 2004; 55: 792-804.

Howard E.I., Sanishvili R., Cachau R.E., Mitschler A., Chevrier B., Barth P., Lamour V., Van Zandt M., Sibley E., Bon C., Moras D., Schneider T.R., Joachimiak A., Podjarny A. Ultrahigh resolution drug design I: Details of interactions in huma aldose reductase – inhibitor complex at 0.66**.** PROTEINS: Struct. Funct. Bioinformat. 2004; 55; 792-804.

Jain A.N. Surflex: Fully automatic flexible molecular docking using a molecular similarity-based search engine. J. Med. Chem. 2003; 46: 499-511.

Jay D., Hitomi H., Griendling K.K. Oxidative stress and diabetic cardiovascular complications. Free Rad. Biol. Med. 2006; 40: 183-192.

Jones G., Willett P., Glen R.C., Leach A.R., Taylor R. Development and validation of a genetic algorithm for flexible docking. J. Mol. Biol. 1997; 267: 727-748.

Jones G., Willett P., Robert C., Glen R.C. Molecular recognition of receptor sites using a genetic algorithm with a description of desolvation. J. Mol. Biol. 1995; 245: 43–53

Jorgensen W.L. Rusting of the lock and key model for protein-ligand binding. Science 1991; 254: 954-955.

Kador P.F. The role of aldose reductase in the development of diabetic complications. Med. Res. Rev. 1988; 8: 325.

King G.L., Brownlee M.B. The cellular and molecular mechanisms of diabetic complications. Endocrinol. Metab. Clin. North Am. 1996; 25: 255-270.

Kinoshita T., Miyake H., Fujii T., Takakurab S., Goto T. The structure of human recombinant aldose reductase complexed with the potent inhibitor zenarestat. Acta Cryst. 2002; 58: 622-626.

Klebe G. Virtual ligand screening: Strategies, perspectives and limitations. Drug Discov. Today 2006; 11: 580-594.

Klebe G., Krämer O., Sotriffer C. Strategies for the design of inhibitors of aldose reductase, an enzyme showing pronounced induced-fit adaptations. Cell. Mol. Life Sci. 2004; 61: 783-793

Kono Y., Kashine S., Yoneyama T., Sakamoto Y., Matsui Y., Shibata, H. Iron chelation by chlorogenic acid as a natural antioxidant. Biosci. Biotechnol. Biochem. 1998; 62: 22-27.

Lee A., Chung S.K., Chun S.S. Demonstration that polyol accumulation is responsible for diabetic cataract by use of transgenic mice expressing the aldose reductase gene in the lens. Proc. Natl. Acad. Sci. 1995; 92: 2780-2784.

Lee Y.S., Chen Z., Kador P.F. Molecular modeling studies of the binding mode of aldose reductase inhibitors at the active site of human aldose reductase. Bioorg. Med. Chem. 1998; 6: 1811-1819.

Miyamoto S. Molecular modeling and structure based drug discovery studies of aldose reductase inhibitors. Chem-Bio. Informatics Journal. 2002; 2: 74-85.

Morris G.M., Goodsell D.S., Halliday R.S., Huey R., Hart W.E., Belew R.K., Olson A.J. Automated docking using a lamarckian genetic algorithm and an empirical binding free energy function. J. Comput. Chem. 1998; 19: 1639-1662.

Morris G.M., Goodsell D.S., Halliday R.S., Huey R., Hart W.E., Belew R.K., Olson A.J. Automated docking using a lamarckian genetic algorithm and an empirical binding free energy function. J. Comput. Chem. 1998; 19: 1639-1662.

Murray C.W., Baxter C.A., Frenkel A.D. The sensitivity of the results of molecular docking to induced fit effects: Application to thrombin, thermolysin and neuraminidase. J. Comput. Aided Mol. Des. 1999; 13: 547-562.

Nakano T., Petrash J.M. Kinetic and spectroscopic evidence for active site inhibition of human aldose reductase. Biochemistry. 1996; 35: 11196-11202.

Oates P.J. The polyol pathway- a culprit in diabetic neuropathy. Neurosc. Research Commun. 1997; 21: 33-40.

Osterberg F., Morris G.M., Sanner M.F., Olson A.J., Goodsell D.S. Automated docking to multiple target structures: Incorporation of protein mobility and structural water heterogeneity in autodock. Proteins 2002; 46; 34-40.

Paul S.B., Choudhury S. Computational analysis of the activity of pongachalcone I against highly resistant bacteria *Pseudomonas putida.* Bioinformation. 2010; 4: 473-477.

Rarey M., Kramer B., Lengauer T., Klebe G. A fast flexible docking method using an incremental construction algorithm. J. Mol. Biol. 1996; 261: 470-489.

Reddy G.B., Satyanarayana A., Balakrishna N., Ayyagari R., Padma M., Viswanath K. Petrash, J.M. Erythrocyte aldose reductase activity and sorbitol levels in diabetic retinopathy. Mol. Vis. 2008; 14: 593.

Rodriguez de Sotillo D.V., Hadle M. Chlorogenic acid modifies plasma and liver concentrations of: cholesterol, triacylglycerol, and minerals in (fa/fa) Zucker rats. J. Nutr. Biochem. 2002; 13: 717-726.

Sato S. Rat-kidney aldose reductase and aldehyde reductase and polyol production in rat-kidney. Am. J. Physiol. 1992; 263: 799-805.

Schnecke V., Kuhn L.A. Virtual screening with solvation and ligand-induced complementarity. Perspect. Drug Des. Discov. 2000*;* 20: 171-190.

Sotriffer C.A., Krämer O., Klebe G. Probing flexibility and ‘‘induced-fit’’ phenomena in aldose reductase by comparative crystal structure analysis and molecular dynamicssimulations. Proteins 2004; 56: 52-66.

Sotriffer C.A., Krämer O., Gerhard Klebe G.Probing flexibility and ‘‘induced-fit’’ phenomena in aldose reductase by comparative crystal structure analysis and molecular dynamicssimulations. Proteins 2004; 56: 52-66.

Sousa S.F., Fernandes P.A., Ramos M.J. Protein-ligand docking: Current status and future challenges. Proteins Struct. Funct. Bioinformat. 2006; 65: 15-26.

Steuber H., Heine A., Klebe G. Structural and thermodynamic study on aldose reductase: nitro-substituted inhibitors with strong enthalpic binding contribution. J. Mol. Biol. 2007; 368: 618–638.

Steuber H., Zentgraf M., Sartini C.M.S., Heine A., Klebe G. Evidence for a novel binding site conformer of aldose reductase in ligand-bound state. J. Mol. Biol. 2007b; 369: 186-197.

Steuber H., Zentgraf M., Sotriffer C.G.C.A., Heine A., Klebe G. Expect the unexpected or caveat for drug designers: Multiple structure determinations using aldose reductase crystals treated under varying soaking and co-crystallisation conditions. J. Mol. Biol. 2006; 363: 174-187.

Steuber H., Zentgraf M., Sotriffer C.G.C.A., Heine A., Klebe G. Expect the unexpected or caveat for drug designers: Multiple structure determinations using aldose reductase crystals treated under varying soaking and co-crystallisation conditions. J. Mol. Biol. 2006; 363: 174-187.

Subramanian J., Sharma S., B-Rao C.A. Novel computational analysis of ligand-induced conformational changes in the ATP binding sites of cyclin dependent kinases J. Med. Chem. 2006; 49: 5434-5441.

Teague S.J. Implications of protein flexibility for drug discovery. Nat. Rev. Drug Discov. 2003; 2: 527-541.

Thomsen R., Christensen M.H. MolDock: A new technique for high-accuracy molecular docking. J. Med. Chem. 2006: 49: 3315-3321.

Thomsen R., Christensen M.H. MolDock: A new technique for high-accuracy molecular docking. J. Med. Chem. 2006; 4:, 3315-3321.

Tomlinson D.R., Stevens E.J., Diemel L. Aldose reductase inhibitors and their potential for the treatment of diabetic complications. Trends Pharm. Sci. 1994; 15: 293-297.

Urzhumtsev A., Tête-Favier F., Mitschler A., Barbanton J., Barth P. Urzhumtseva L. Biellmann J.F., Podjarny A.D., Moras D. A ‘specificity’ pocket inferred from the crystal structures of the complexes of

aldose reductase with the pharmaceutically important inhibitors tolrestat and sorbinil. Structure 1997; 5: 601-612.

Van den Enden M.K.; Nyengaard J.R., Ostrow E. Burgan, J.H. Williamson, J.R. Elevated glucose levels increase retinal glycolysis and sorbitol pathway metabolism. Invest. Ophthalmol. Vis. Sci. 1995; 36: 1674-1685.

Van Zandt M.C., Doan B., Sawicki D.R., Sredy J., Podjarny A.D. Discovery of [3-(4,5,7-trifluoro-benzothiazol-2-ylmethyl)-pyrrolo [2,3-b] pyridin-1-yl]acetic acids as highly potent and selective inhibitors of aldose reductase for treatment of chronic diabetic complications. Bioorg. Med. Chem. Lett. 2009; 19: 2006-2008.

Wilson D.K., Bohren K.M., Gabbay K.H., Quiocho F.A. An unlikely sugar substrate site in the 1.65 A structure of the human aldose reductase holoenzyme implicated in diabetic complications. Science 1992; 257: 81-84.

Wilson D.K., Tarle I., Petrash J.M., Quiocho F.A. Refined 1.8 Å structure of human aldose reductase complexed with the potent inhibitor zopolrestat. Proc. Natl. Acad. Sci. USA 1993; 90: 9847-9851.

Yabe-Nishimura C. Aldose reductase in glucose toxicity: A potential target for the prevention of diabetic complications. Pharmacol. Rev. 1998; 50: 21-33.

Yang J.M., Chen C.C. GEMDOCK: a generic evolutionary method for molecular docking. Proteins: Struct. Funct. Genet 2004; 55: 288-304.

How to cite this article:

Sadaf Naeem, Peter Hylands and David Barlow., Docking Studies of Chlorogenic Acid against Aldose Redutcase by using Molgro Virtual Docker Software. J App Pharm Sci. 2013; 3 (01): 013-020.