

Molecular Docking Evaluation of Some Natural Phenolic Compounds as Aldose Reductase Inhibitors for Diabetic Complications

AJMER SINGH GREWAL*, NEELAM SHARMA, SUKHBIR SINGH AND SANDEEP ARORA

Chitkara College of Pharmacy, Chitkara University, Rajpura, Patiala, 140401, Punjab, India

*Email: ajmergrewal2007@gmail.com

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Abstract The enzyme aldose reductase (AR) is a member of aldoketoreductase super-family which catalyzes the formation of sorbitol from glucose through polyol pathway of glucose catabolism. Reduced sorbitol production via polyol pathway due to AR inhibition is a target of choice for controlling major complications of diabetes. Epalrestat is the only commercially available inhibitor of AR till date, thus, there is a great need to search for more economical, nontoxic and safer inhibitors of AR enzyme. Flavonoids, the polyphenol compounds in plants have been reported for inhibitory effects against AR. The objective of this study is to explore the binding modes of natural phenolic compounds with AR to design safer natural drugs as alternatives to synthetic drugs. We conducted a molecular docking study on some natural phenolic compounds with AR enzyme in complex with the synthetic inhibitor. The overlay of the docked pose of the selected natural phenols with the AR-reference inhibitor complex showed that the selected natural compounds have the similar binding pattern with the active site residues of the enzyme as that of co-crystallized inhibitor. The results of docking study showed the best binding affinity of AR with that of 2-(4-hydroxy-3-methoxyphenyl) ethanoic acid and butein, having the lowest binding free energy of -9.8 kcal/mol and -9.7 kcal/mol, respectively. This information can be utilized to design potent, economical and non-toxic natural AR inhibitors from natural phenols for the therapeutics of diabetic complications.

Keywords: Aldose Reductase, AR Inhibitors, Diabetic Complications, Flavonoids, Molecular Docking, Phenolic compounds, Polyol Pathway.

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1. INTRODUCTION

Diabetes mellitus (often called as diabetes) is a cluster of metabolic conditions due to defect in insulin secretion, insulin action, or both resulting in prolonged hyperglycemia and defective metabolism of food. According to etiological classification, Type 1 diabetes (also called as insulin dependent diabetes mellitus or juvenile-onset diabetes, occurs due to defect in the β -cells of pancreas, resulting in lack of insulin) and Type 2 diabetes (also called as non-insulin dependent diabetes mellitus or adult-onset diabetes, occurs due to defect in insulin action) are two most important types of diabetes (American Diabetes Association, 2014; Grewal *et al.*, 2014). As per the latest data from International Diabetes Federation, in 2013 there were 382 million diabetic patients, and in 2035 the number of diabetic patients may approach 600 million. Diabetes is the major contributor to the mortality worldwide, especially in the developing countries and the latest figures pointed out diabetes as a key obstacle in the overall development worldwide. Diabetes has become the major health problem worldwide, and has been pointed out as crucial importance in community health due to various complications linked with it (International Diabetes Federation, 2013; Wild *et al.*, 2004; Olokoba *et al.*, 2012; Mohan & Anbalagan, 2013). The main effect of lack of insulin or insulin resistance is the defective metabolism of glucose in the cells of body resulting in increased glucose concentration in blood, and increased metabolism of fats and proteins (Kohei, 2010). The diabetic complication result due to long-lasting increased blood glucose levels resulting in injury to blood vessels and peripheral nerves. The major diabetic complications are classified as microvascular (diabetic neuropathy, nephropathy, retinopathy, and cataracts) and macro vascular complications (defects in cardiovascular and cerebrovascular system) (Cade, 2008). The various mechanisms had been proposed for diabetic complications including polyol pathway, larger production of advanced glycation end products, augmented production of diacylglycerol due to hyperglycemia, altered catabolism of extra glucose through hexosamine pathway and defect in antioxidant mechanism due to hyperglycemia. The polyol pathway is the most accepted mechanism of crucial significance for the pathogenesis of complications of diabetes. The activated polyol pathway leads to enlarged buildup of sorbitol in cells causing osmotic tension on the cells which harms the proteins of cell membrane via various oxidative mechanisms (Forbes & Cooper, 2013).

Aldose Reductase (AR) is a member of the aldo-ketoreductase superfamily of enzymes which catalyzes the formation of sorbitol from glucose, the very first and most important rate-determining reaction of the polyol pathway

(Yabe-Nishimura, 1998; Oates, 2008). Under normal conditions glucose is catabolized via glycolysis and Kreb's cycle leading to formation of building blocks and energy for cellular functions.

In case of hyperglycemia, higher glucose concentration stimulates AR resulting in metabolism of glucose by activated polyol pathway. AR reduces that glucose to sorbitol, which is later oxidized to fructose. In the process of reducing high intracellular glucose to sorbitol, AR consumes the cofactor NADPH (an important co-factor involved in production of an important antioxidant, glutathione, resulting in decreased glutathione levels). Osmotic stress due to accumulation of extra sorbitol and oxidative stress due to decrease in NADPH/NADP⁺ ratio and reduced NAD⁺ leads to reduced cellular antioxidant capacity. Increased production of sorbitol catalyzed by AR in polyol pathway accumulates in cells and is difficult to diffuse through the cell membranes, which increases osmotic stress to cells leading to the development of diabetic complications. The accumulation of sorbitol through increased activity of AR in lens, retina, and sciatic nerves result in retinopathy, neuropathy, and nephropathy, respectively (Forbes & Cooper, 2013; Brownlee, 2001; Chung & Chung, 2005). The polyol pathway can be targeted by inhibiting the enzyme AR resulting in the reversal of the osmotic stress caused by activated polyol pathway. Thus, reduction of the polyol pathway by AR inhibitors has been a potential therapeutic target in the treatment and prevention of diabetic complications. Numerous AR inhibitors have been advanced as drug candidates for the treatment and prevention of diabetic complications (Oates, 2008; Brownlee, 2001; Suzen & Buyukbingol, 2003; Cumbie & Hermayer, 2007). The AR inhibitors developed vary structurally including carboxylic acid derivatives, spirohydantoin and related cyclic amides, nitromethane derivatives, sulfonamides, thiazolidinediones, benzodiazepines, and phenolic derivatives (related to benzopyran-4-one and chalcone). Even though numerous clinical trials for the treatment of diabetic complications have been conducted over the past two decades with synthetic compounds, pharmacokinetic problems connected to these AR inhibitors, together with the length of trials, have resulted in the lack of observed efficacy (Jain *et al.*, 2012; Grewal *et al.*, 2016). Among these AR inhibitors, epalrestat is the only commercially available inhibitor till date. Thus, there is still an urgent need for new and safe AR inhibitors. Several potent inhibitors of AR from natural sources have been reported which are obtained from terrestrial, micro-organism, and marine sources for their role in the treatment and prevention of diabetic complications. AR inhibitors obtained from natural sources include flavonoids and phenolic compounds, alkaloids, terpenoids, coumarin

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derivatives, and vitamin C (Grewal *et al.*, 2016; Fuente & Manzanaro, 2003; Nakai *et al.*, 1985). Numerous flavonoids like rutin, kaempferol, quercetin, and quercetrin had shown excellent anti-diabetic potential by AR inhibition (Lee *et al.*, 2015; Zhang *et al.*, 2016). Some natural phenolic compounds were chosen for the docking study from the recent literature having potent AR inhibitory activity including nepetin (Tomás-Barberán *et al.*, 1986), epicatechingallate (Murara *et al.*, 1994), Capillarisin (Okada *et al.*, 1995), isorhamnetin-3,7-disulfate (Haraguchi *et al.*, 1996), Luteolin (Yoshikawa *et al.*, 1999), Protocatechualdehyde (Goodarzi *et al.*, 2006), Davidigenin (Logendra *et al.*, 2006), curcumin (Muthenna *et al.*, 2009), 2-(4-hydroxy-3-methoxyphenyl)ethanoic acid (Kato *et al.*, 2006), Quercetin (Chethan *et al.*, 2008), butein (Lee *et al.*, 2008), desmethylanthydroicaritin (Jung *et al.*, 2008) and semilicoisoflavone B (Lee *et al.*, 2010).

The aim of this study is the *in silico* evaluation of selected natural phenolic compounds in order to establish the structural basis of their AR inhibitory activity and to investigate the binding modes of the selected compounds in active site of AR to design safer natural drugs as alternatives to synthetic drugs using molecular docking.

2. EXPERIMENTAL

Molecular docking was performed for the selected natural phenolic compounds in the binding site of AR protein in AutoDockVina (Trott & Olson, 2010) and the graphical user interface, AutoDock Tools (Morris *et al.*, 2009) installed on Windows 7 computer.

2.1 Preparation of Ligand Molecules

The 2-D chemical structures of the ligands were prepared by MarvinSketch (Marvin 15.9.21, 2015, ChemAxon) and converted to 3-D by Frog2 server based on a graph decomposition of the compounds coupled with an identification of the stereo-centres for which the chirality is unspecified (Miteva *et al.*, 2010). The ligands were converted to PDBQT files from MOL format using AutoDock Tools.

2.2 Preparation of Protein Molecule

After assessing a numbers of co-crystallized structures of AR protein available in the RCSB protein data bank (<http://www.rcsb.org/pdb>), the best ligand bound complexes (PDB entry: 4LBS) was selected with complexes having maximum resolution and best binding interactions between ligands and

proteins. The PDB files of the target protein was edited using PyMOL (The PyMOL Molecular Graphics System, Version 1.7.4.5 Edu, Schrödinger, LLC.) by removing complexed inhibitor, all the water molecules as well as all non-interacting ions. The PDBQT file of AR proteins was generated from the PDB files using AutoDock Tools and all the polar hydrogen atoms were added to the protein molecule.

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2.3 Preparation of Configuration Files

The “Grid” of AutoDock Tools was used for calculating the grid parameters and all the data regarding target protein, ligand, grid size and geometry were saved in TXT file. The grid size was set to $32 \times 32 \times 32$ xyz points with grid spacing of 0.375 Å and grid center was designated at dimensions (x, y, and z): 9.568, 0.111, and 0.097. The exhaustiveness was set at 8 and scoring grid was calculated from the ligand structure to reduce the computation time.

2.4 Docking Method

The reference ligand, (2-((4-bromo-2,6-difluorobenzyl)carbamoyl)-5-chlorophenoxy) acetic acid was docked in the active site of target proteins and compared with that of the co-crystallized inhibitor of AR (PDB ligand of 4LBS) for determining the accuracy of the docking protocol. The prepared ligand molecules were docked in the active site of the refined AR model utilizing AutoDockVina and scored by using scoring function. The binding free energy (ΔG , kcal/mol) for each ligand was reported in log file. PyMOL was utilized for the analysis of the binding interactions (including H-bond and hydrophobic interactions) of the ligands in the active site of target proteins.

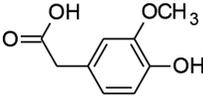
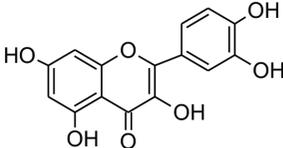
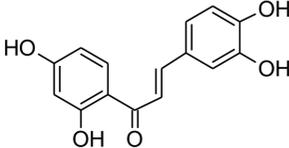
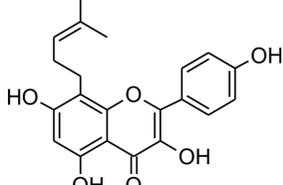
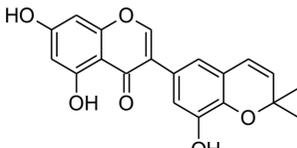
3. RESULTS AND DISCUSSION

The names and chemical structures of the natural phenolic compounds selected for the molecular docking study are presented in Table 1 along with their source and reported AR inhibitory activity in terms of IC_{50} value (concentration causing 50% inhibition of the AR activity). *In silico* studies were performed to explore the affinity and binding interactions of the selected natural phenolic compounds in the active site of AR protein (PDB entry: 4LBS). The reference ligand was docked into the active site of AR protein; and the docked reference inhibitor of AR produced a similar binding pattern and superposition on the binding mode of co-crystallized inhibitor with ΔG of -9.2 kcal/mol validating accuracy of docking methodology.

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Table 1: Structures of natural phenolic compounds selected for docking study with their source and reported AR inhibitory activity.

Comp.	Name	Chemical structure	Remarks
1	Nepetin		Obtained from <i>Eupatorium ballotaefolium</i> with 95% AR inhibition
2	Epicatechingallate		Obtained from green tea (<i>Camellia sinensis</i>) leaves with $IC_{50} = 38 \mu M$
3	Capillarisin		Obtained from <i>Artemisia capillaris</i> with $IC_{50} = 0.22 \mu M$
4	Isorhamnetin-3,7-disulfate		Obtained from <i>Polygonum hydropiper</i> with $IC_{50} = 1.8 \mu M$
5	Luteolin		Obtained from <i>Chrysanthemum indicum</i> $IC_{50} = 0.45 \mu M$
6	Protocatechualdehyde		Obtained from <i>Ganoderma applanatum</i> $IC_{50} = 0.7 \mu M$
7	Davidigenin		Obtained from <i>Artemisia dracunculus</i> with $IC_{50} = 12.70 \mu M$
8	Curcumin		Obtained from <i>Curcuma longa</i> with $IC_{50} = 6.8 \mu M$

Comp.	Name	Chemical structure	Remarks	Molecular Docking Evaluation of Some Natural Phenolic Compounds as Aldose Reductase Inhibitors for Diabetic Complications
9	2-(4-Hydroxy-3-methoxyphenyl)ethanoic acid		Obtained from <i>Zingiberofficinale</i> with $IC_{50} = 18.5 \mu M$	
10	Quercetin		Obtained from <i>Eleusinecoracana</i> with $IC_{50} = 14.8 nM$	
11	Butein		Obtained from <i>Rhusverniciflua</i> with $IC_{50} = 0.5 \mu M$	
12	Desmethylanhydroicaritin		Obtained from <i>Sophoraflavescens</i> with $IC_{50} = 0.95 \mu M$	
13	Semilicoisoflavone B		Obtained from <i>Glycyrrhizauralensis</i> with $IC_{50} = 1.8 \mu M$	

In this study 13 different natural phenolic compounds were selected for molecular docking studies. The drug-likeness properties including molecular weight, partition coefficient i.e., log P, hydrogen bond donors i.e., HBD, and hydrogen bond acceptors i.e., HBA were computed for the selected natural phenols. Most of the compounds selected for *in silico* studies showed drug-like properties as contrived by Lipinski's rule of five (presented in Table 2). All the selected natural phenolic molecules were docked in the active site of human AR protein (PDB entry: 4LBS). Most of the compounds showed appreciable binding pattern in the active site of AR protein as established by analyzing their bonding interactions in terms of H-bond, hydrophobic interactions and ΔG of the best docked poses (Table 2).

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Table 2: Molecular properties, interacting amino acids, distance and ΔG of the selected natural phenolic compounds.

Comp.	Mol. Wt.*	Log P*	HBA*	HBD*	Interacting amino acid (s)	Distance (Å)	ΔG
1	316	1.6	7	4	His110, Trp111	3.6, 3.1	-8.6
2	442	3.7	9	7	Tyr48, His110, Trp111	3.2, 2.6, 4.0	-8.9
3	316	2.8	7	3	Tyr48, His110	4.2, 3.2	-8.0
4	475	2.0	11	4	Tyr48, His110, Trp111	3.8, 3.3, 3.0	-8.9
5	286	2.4	6	4	Trp111	3.8	-8.1
6	138	1.2	3	2	Trp111	4.8	-6.0
7	258	3.4	4	3	Tyr48	4.7	-8.5
8	368	4.0	6	2	His110, Trp111	3.2, 3.2	-8.2
9	182	1.1	4	2	Tyr48, His110, Trp111	2.8, 3.1, 2.9	-9.8
10	302	1.7	7	5	Trp111	3.9	-8.1
11	272	3.4	5	4	Tyr48, His110, Trp111	3.2, 2.8, 3.2	-9.7
12	368	4.0	6	4	Trp111	2.9	-7.2
13	352	4.2	6	3	Trp111	3.3	-7.3

*Mol. Wt., Log P, HBA, and HBD were calculated using MarvinSketch (2015).

Based on the lowest docking free energy and better binding interactions in the active site of AR protein, compounds **2**, **4**, **9**, and **11** were further analyzed in details by PyMOL. The receptor-ligand complexes produced after docking of the selected natural phenolic compounds were analyzed in terms of H-bond interactions, hydrophobic interactions, binding free energy and orientation of the docked compounds in the active site of AR protein. These parameters show a chief role in the biological activity of a compound. The docked poses of the natural phenolic compounds were ranked based on the docking scores i.e. the lowest binding free energy and only the top ranked and best fitted conformations of the selected natural phenolic compounds were analyzed for the study. The overlay of the selected compounds (**2**, **4**, **9**, and **11**) with that of reference inhibitor in the binding site of AR showed similar binding mode as that of the reference ligand (Figure 1).

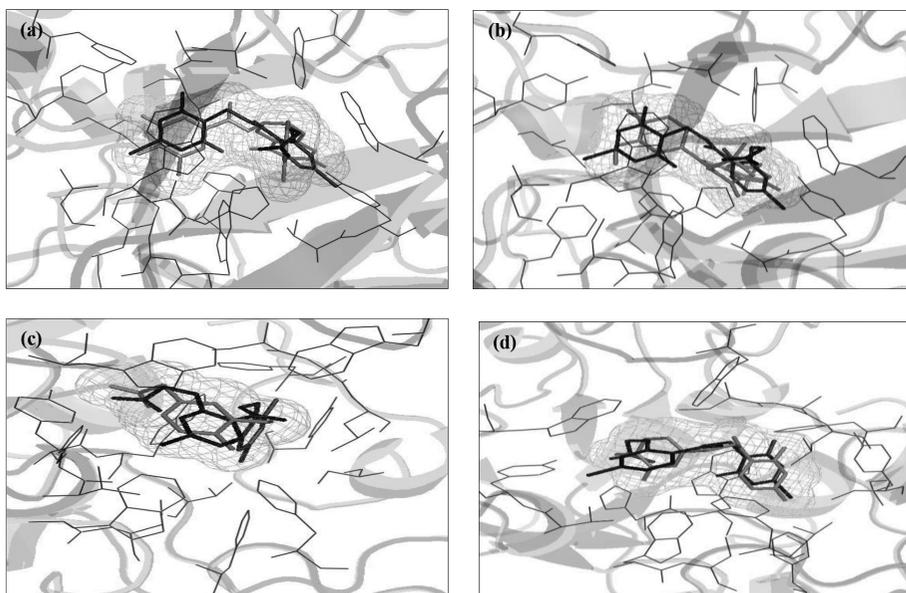


Figure 1: Overlay of compounds (black) **2** (a), **4** (b), **9** (c) and **11** (d) with PDB ligand 4LBS (grey) in the binding site of AR protein.

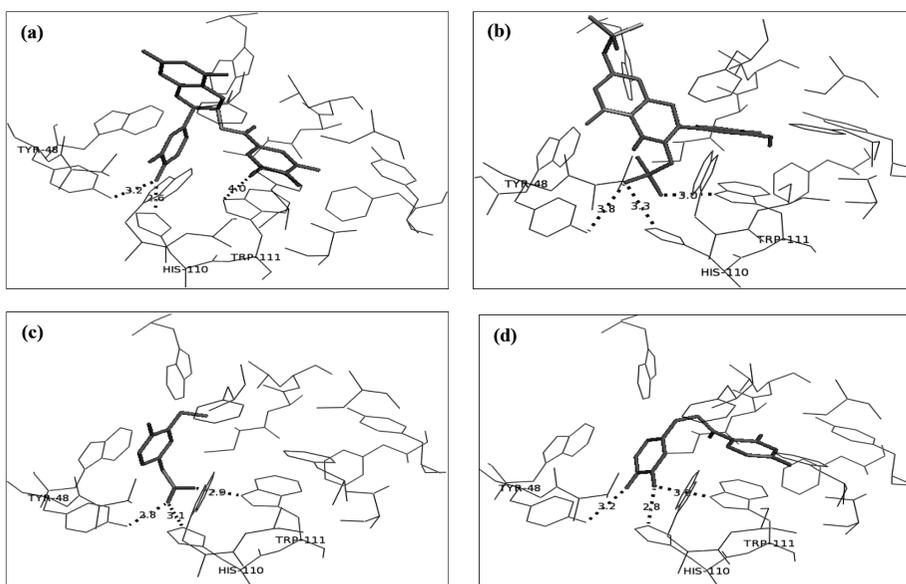


Figure 2: Docked pose showing H-bond interactions for the compounds **2** (a), **4** (b), **9** (c) and **11** (d) in binding site of AR protein.

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The docked pose of compound **2** showed the H-bond interactions between the phenolic OH of compound **2** and OH of Tyr48, NH of His110 and NH of Trp111 in binding site of AR protein with H-bond distance of 3.2, 2.6 and 4.0 Å respectively (Figure 2a). The docked pose of compound **4** showed the H-bond interactions between the alcoholic OH and OH of Tyr48, NH of His110 and NH of Trp111 in binding site of AR protein with H-bond distance of 3.8, 3.3 and 3.0 Å respectively (Figure 2b). The docked pose of compound **9** showed the H-bond interactions between the carbonyl and OH of Tyr48, NH of His110 and NH of Trp111 in binding site of AR protein with H-bond distance of 2.8, 3.1 and 2.9 Å respectively (Figure 2c). The docked pose of compound **11** showed the H-bond interactions between the phenolic OH and OH of Tyr48, NH of His110 and NH of Trp111 in binding site of AR protein with H-bond distance of 3.2, 2.8 and 3.2 Å respectively (Figure 2d). This demonstrates that the selected natural phenolic compounds possess the functional groups required for effective binding with the active site residues when compared with the standard PDB ligand.

The best binding affinity of AR protein was found with the compounds **9** (2-(4-hydroxy-3-methoxyphenyl)ethanoic acid) and **11** (butein) in the complex of AR with binding free energy of -9.8 kcal/mol and -9.7 kcal/mol, respectively. Other natural phenolic compounds such as compounds **2** (epicatechingallate) and **4** (isorhamnetin-3,7-disulfate) also represent good binding affinity with AR protein as indicated in Table 2. All these docking results and overlay of docked natural phenols with the PDB ligand 4LBS revealed that the selected natural phenols have a potential to inhibit AR enzyme.

4. CONCLUSION

Molecular docking studies using AutoDock vina and AutoDock Tools was performed to explore the binding mechanism of the selected natural phenolic compounds with AR enzyme. In the present molecular modeling study, results clearly demonstrated that the selected natural phenolic compounds have a similar binding sites and interactions with AR as those of the synthetic drug taken for the study and prove that dietary flavonoids (phenolic compounds) may possess properties useful for the control of diabetic complications. Thus *in silico* study is actually an added advantage to screen the AR inhibition and natural phenolic compounds may serve as useful leads for the synthesis of clinically useful and safe inhibitors of AR for therapeutics of diabetic complications. The results of docking study revealed that 2-(4-hydroxy-3-methoxyphenyl)ethanoic acid and 11 (butein) have strongest binding with the AR protein with binding free energy of -9.8 kcal/mol and -9.7 kcal/mol, respectively. Structural modifications and further studies on these natural

phenolic compounds are required to develop safe and potent AR inhibitors for the management of various diabetic complications.

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