ORIGINAL ARTICLE

Integrated *in silico* molecular docking and *in vitro* evaluation of phytoconstituents as aldose reductase inhibitors for diabetes management

Gaurav Sarsodia[1,2], Raghvendra Dubey[1], Kushagra Dubey[3]

[1]Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Sciences, Sage University, Indore, Madhya Pradesh, India, [2]Department of Pharmaceutical Chemistry, Indore Institute of Pharmacy, Indore, Madhya Pradesh, India, [3]Department of Pharmaceutical Chemistry, Smriti College of Pharmaceutical Education, Indore, Madhya Pradesh, India

Abstract

Aims: This study aims to evaluate the *in vitro* antidiabetic potential of selected phytoconstituents belonging to alkaloidal amide, flavone, saponin, and alkaloid classes, and to investigate their potential role in modulating insulin-related activity, thereby elucidating their therapeutic relevance in diabetes management. **Materials and Methods:** Through *in silico* and *in vitro* methods, possible aldose reductase (AR) inhibitors were identified using a phytoconstituent database collected from plants. To estimate the binding energy and interaction key of the residues, a molecular library comprising representative phytochemicals of the alkaloidal amide, flavone, saponin, and alkaloid classes was created and utilized for molecular docking-based virtual screening against human AR. Candidates were chosen based on their docking results for experimental validation. Candidates were chosen based on their docking results for experimental validation. A sample cuvette containing 0.3 mL of enzyme extract, 0.5 mL of nicotinamide adenine dinucleotide phosphate (0.104 mM), 0.75 mL of sodium phosphate buffer (0.1 M, pH 6.2), 0.1 mL of phytoconstituents, and 0.7 mL of deionized water was used to measure the AR inhibitory activity. Using *in vitro* anti-diabetic models, assays were conducted. A spectrophotometric enzyme inhibition assay was used to measure the *in vitro* AR inhibitory activity. The antidiabetic potential was assessed by calculating the IC_{50} values and the percentage of inhibition. **Results:** Strong binding affinities and advantageous interactions between a number of phytoconstituents and the AR active site were found by molecular docking studies, indicating the potential for their inhibitory effects. Subsequent *in vitro* evaluation confirmed significant, dose-dependent AR inhibition by selected compounds, with aegelin, quercetin, piperine, apigenin, and chrysin exhibiting the highest inhibitory activities and low IC_{50} values. The inhibition of AR enzyme activity was tested at doses ranging from 100 to 700 µg/mL. Aegelin, quercetin, piperine, apigenin, and chrysin showed the highest levels of inhibition (87.18, 86.67, 86.33, 85.77, and 81.13%, respectively). The concordance between computational predictions and experimental findings validates the screening strategy and highlights the relevance of these phytoconstituents as potential modulators of glucose metabolism and diabetic complications. **Conclusion:** The present study demonstrates that an integrated molecular docking and *in vitro* evaluation approach is effective in identifying promising plant-derived AR inhibitors. The findings highlight selected phytoconstituents as potential lead candidates for the development of safer, natural antidiabetic therapeutics.

Key words: Aldose reductase inhibition, diabetes mellitus, *in vitro* antidiabetic activity, molecular docking, phytoconstituents

INTRODUCTION

Diabetes, a chronic, frequently hereditary disease that affects the hormone system, can have a major negative influence on one's health and even be fatal. It is characterized by elevated blood sugar levels, which ultimately result in urine that contains sugar.

Address for correspondence: Gaurav Sarsodia, Indore Institute of Pharmacy, Indore, Madhya Pradesh, India. Phone: +91-9424015233. E-mail: gauravsarsodia@gmail.com

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Reduced nicotinamide adenine dinucleotide phosphate (NADPH) is necessary for the monomeric enzyme aldose reductase (AR), which is a member of the aldo-keto reductase superfamily. Sorbitol and galactitol, two polyols produced by AR, build up in the lens of the eye. Sorbitol accumulation in the lens due to AR -catalyzed glucose reduction causes osmotic swelling, ionic imbalance, and protein insolubilization, all of which contribute to cataractogenesis. In addition, hyperglycemic damage linked to diabetes retinopathy, nephropathy, and neuropathy may be explained by a similar series of events. Structural studies that demonstrate the absence of ionic residues typical of carbohydrate-binding proteins in the AR active site lend credence to the enzyme's role in detoxification.

An effective *in silico* drug design method for predicting the potential target protein binding site for a ligand is molecular docking. Using a virtual screening method, a large number of compounds are narrowed down to a small number of molecules with strong receptor binding affinities. To find a suitable ligand for the binding pockets with the lowest energy conformation, the docking process uses a computational approach. The objective of this study is to identify phytoconstituents with potential AR inhibitory activity.[1,2]

EXPEROMENTAL METHODS

Computational studies

Ligand library preparation

A molecular ligand library comprising 85 phytoconstituents was constructed by selecting compounds from diverse plant sources, including alkaloids, flavonoids, glycosides, saponins, and terpenoids, based on an extensive survey of the published literature reporting their traditional use and potential relevance in diabetes management.[3] These phytochemicals were chosen due to their documented bioactivity and structural diversity, which may contribute to effective AR inhibition.[4]

The chosen ligands' two-dimensional (2D) structures were obtained in SDF format from the PubChem database. Structure preparation and energy minimization were performed using Chem3D Ultra (version 9.0), employing the MM2 force field with default convergence criteria to obtain stable three-dimensional (3D) conformations. After the optimized ligand structures were transferred to PDB format, AutoDock Tools (version 1.5.6) was used to add polar hydrogen atoms and assign Gasteiger charges in order to further prepare them for docking. Finally, all ligands were stored in PDBQT format for use in ensuing molecular docking analyses. This standardized ligand preparation protocol ensured structural accuracy, consistency, and reproducibility of the computational workflow.

Macromolecular target selection and preparation

AR, a member of the aldo-ketoreductase superfamily and a monomeric reduced NADPH-dependent enzyme, inhibits tissue plasminogen activation by interfering with serine protease activity, which delays the healing of diabetic tissues. A protein called aldose reducase is essential for controlling the healing process of wounds. The main function of this protein is to regulate the activity of plasminogen activators, which are enzymes that break up blood clots and promote tissue healing.[5,6] Thus, aldose reductase is an important target for the treatment of diabetes, and in ongoing study, we are trying to identify novel plant-based inhibitors of AR that can be used in the treatments of complex diabetes.[7,8] A 3D model of AR complexed with an antagonist AZ3976 (pdb id: 3s3g) was procured from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) database.[9,10] To do docking research, the structural model of AR and the complexed reference ligand was extracted by deleting each of them separately. This created a nascent receptor and ligand molecule.

Molecular docking-based screening

The chosen phytoconstituents binding affinities and interaction patterns with the human AR receptor were assessed using molecular docking techniques. The AutoDock Tools (ADT, version 1.5.6) were used to construct the ligand and protein receptor structures before docking. In order to treat the receptor, polar hydrogen atoms were added, Gasteiger charges were assigned, and water molecules and co-crystallized ligands were eliminated. After that, the prepared receptor was stored in PDBQT format. Likewise, ADT was used to protonate, assign Gasteiger charges, and convert the energy-minimized ligands to PDBQT format.[11,12] To estimate ligand–receptor binding conformations and binding energies, docking simulations were performed using AutoDock 4.2. The reference ligand (AZ3976) was redocked into the AR active site to validate the docking methodology. The reproducibility of the docking parameters was then evaluated by comparing the resulting docked pose with the crystallographic conformation. The consistency in binding orientation and interaction patterns between the redocked and native ligand confirmed the validity of the docking setup.[11-14] Following validation, the optimized docking parameters were employed to perform virtual screening of the prepared herbal-based ligand library against the AR receptor. Predicted binding energies and important interactions with active-site residues were used to rank the docked complexes. For additional *in vitro* testing, compounds with the best binding scores and interaction patterns were selected as possible AR inhibitors (ARIs).[15-22]

In vitro antidiabetic evaluation

The procured phytoconstituents is subjected to anti-diabetic evaluation of as following protocols.

Enzyme preparation

The lenses were quickly removed from recently killed goat eyeballs that were purchased from a nearby slaughterhouse. To separate the insoluble material, 100–200 g of lenses were homogenized with three volumes of cold distilled water using a homogenizer. The lenses were then centrifuged at 10,400 RPM for 15 min at 0–4°C. After that, saturated ammonium sulfate was added to the supernatant until 40% saturation was reached. To achieve full precipitation, the resulting dense suspension was centrifuged, and the precipitate was collected after standing for 15 min with occasional stirring. After that, saturated ammonium sulfate was added to the supernatant until 40% saturation was reached. To achieve full precipitation, the resulting dense suspension was centrifuged, and the precipitate was collected after standing for 15 min with occasional stirring. The mixture was centrifuged after the ammonium sulfate content was increased to 50% saturation to further remove inactive proteins. Compared to a single precipitation stage, this two-step method allowed for a more efficient separation of AR activity from contaminating proteins. The enzyme was then recovered by centrifugation after AR was precipitated from the 50% supernatant by adding powdered ammonium sulfate to reach 75% saturation. The enzymatic test was performed using the resultant precipitate.[1,21]

Assay for AR inhibition

The sample cuvette was made using a mixture of 0.3 mL enzyme extract, 0.5 mL NADPH (0.104 mM), 0.75 mL sodium phosphate buffer (0.1 M, pH 6.2), 0.1 mL phytoconstituents, and 0.7 mL deionized water to assess AR inhibitory activity. Following ten minutes of incubation at 30°C, 0.75 mL of D, L-glyceraldehyde (10 mM) was added as the substrate to the reaction mixture. Then, using a reference cuvette that contained every component except D, L-glyceraldehyde, absorbance was measured at 340 nm for 3 min at 30-s intervals. The standard was quercetin. The experiment was performed in triplicate, and the dose-response curve was used to calculate the IC_{50} value and the percent inhibition.

RESULTS AND DISCUSSION

Computational studies

Design of ligand library

A structurally diverse herbal-based ligand library comprising 85 phytoconstituents was designed by selecting compounds from different chemical classes, including alkaloids, flavonoids, glycosides, saponins, terpenoids, steroidal compounds, and polyphenols. These phytochemicals were sourced from medicinal plants traditionally used for the management of diabetes and its associated metabolic complications, as supported by literature evidence.

The 2D structures of each ligand were retrieved from the PubChem database using their isomeric SMILES representations and were drawn and verified using ChemDraw Ultra (version 9.0). In order to achieve stable conformations, 3D structures were then created and put through energy minimization using Chem3D Ultra with the MM2 force field. Molecular docking-based virtual screening against the AR enzyme, a crucial target linked to the polyol pathway and diabetes consequences, was conducted using the optimized ligand structures. This methodical approach to ligand design guaranteed structural variety and applicability to the study's antidiabetic goal.

Target selection (AR)

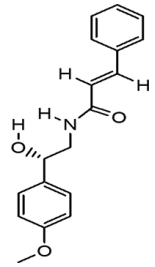
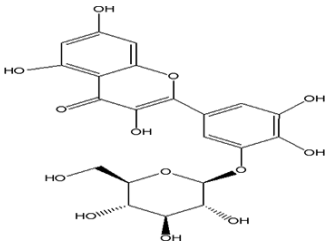
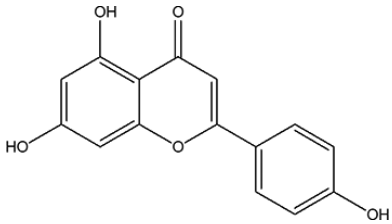
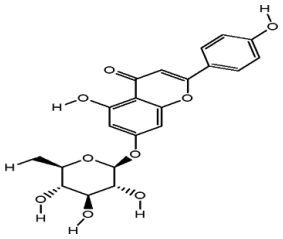
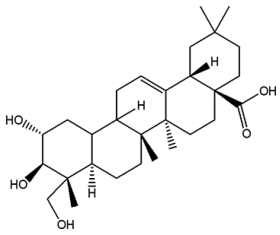
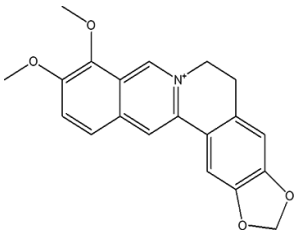
AR is a cytosolic NADPH-dependent enzyme belonging to the aldo–keto reductase superfamily, and plays a pivotal role in the polyol pathway of glucose metabolism. Under hyperglycemic conditions, AR catalyzes the reduction of glucose to sorbitol, leading to intracellular sorbitol accumulation, osmotic stress, and oxidative damage, which are key contributors to diabetic complications such as neuropathy, retinopathy, and nephropathy. Consequently, AR is a well-established molecular target for the development of antidiabetic therapeutics. The 3D crystal structure of human AR was retrieved from the RCSB PDB, solved by X-ray diffraction at a resolution of 2.40 Å. The enzyme structure consists of a single polypeptide chain comprising 383 amino acids, characteristic of its monomeric functional form. Before docking studies, the co-crystallized ligand and crystallographic water molecules were removed to obtain the nascent receptor structure. The prepared protein was subsequently used for molecular docking-based virtual screening to identify potential phytoconstituent inhibitors targeting the active site of AR.[7,20]

Molecular docking

The co-crystallized reference ligand (AZ3976) was redocked into the human AR receptor's active site using AutoDock 4.2 to confirm the molecular docking procedure used in this investigation. The binding interactions of emodin with human aldose reductase are illustrated in Figure 1, highlighting the general binding mode within the enzyme active site.

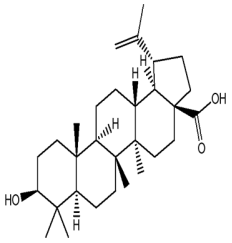
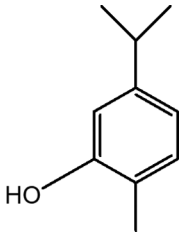
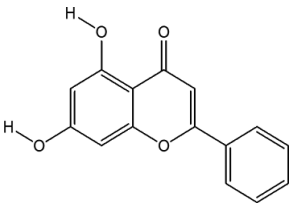
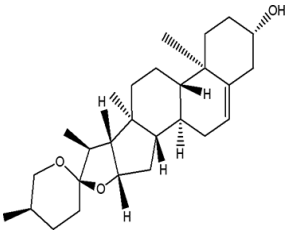
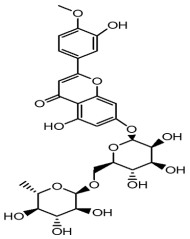
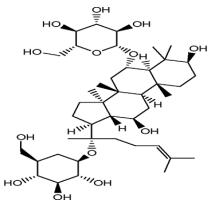
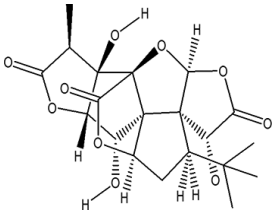
The redocked pose of AZ3976 closely overlapped with its crystallographic conformation, indicating reliable reproduction of the experimentally observed binding orientation. The predicted binding energy for the reference ligand was found to be within an acceptable range, confirming the suitability of the selected grid parameters and docking settings for subsequent virtual screening. Following protocol validation, the prepared ligand library comprising 85 phytoconstituents was subjected to molecular docking–based virtual screening against the AR active site using the same validated parameters. The docked ligands were ranked based on their predicted binding energies and key interactions with

Table 1: Binding score and interacting residues for the shortlisted leads against aldose reductase receptor

S. No.	Ligand	Structure	Binding Energy (kcal/moL)
			Aldose reductase (PDB: 3s3g)
1.	Aegelin		**–9.20**
2.	Andmyricetin-3-glucoside		–7.66
3.	Apigenin		**–8.59**
4.	Apigenin-7-O-glucoside		**–8.46**
5.	Arjunolic acid		–4.08
6.	Berberine		**–7.71**

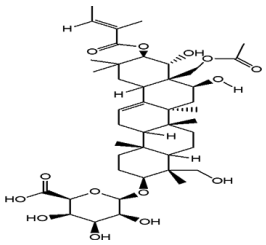
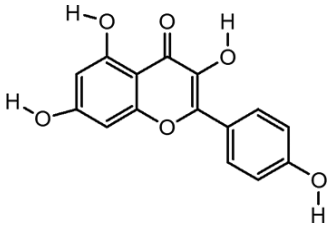
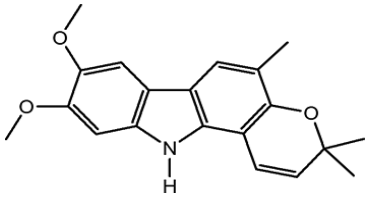
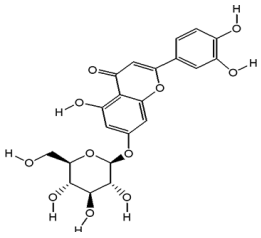
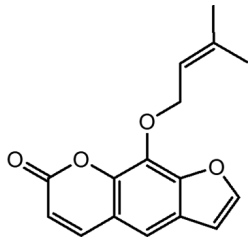
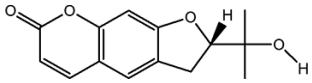
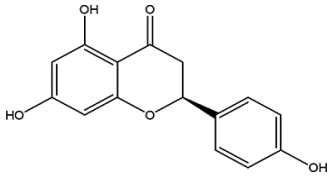
(Contd...)

Table 1: *(Continued)*

S. No.	Ligand	Structure	Binding Energy (kcal/moL)
			Aldose reductase (PDB: 3s3g)
7.	Betulinic acid		**–4.90**
8.	Carvacrol		–6.72
9.	Chrysin		**–8.94**
10.	Diosgenin		-
11.	Diosmin		–4.77
12.	Geinoside		-
13.	Ginkgolides		–4.45

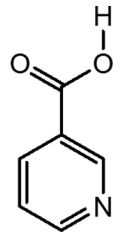
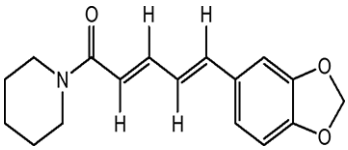
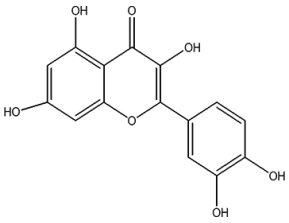
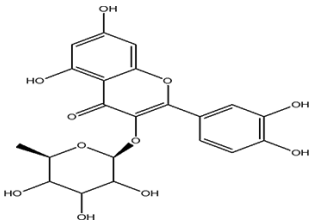
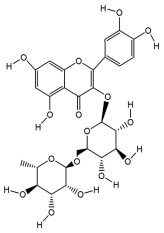
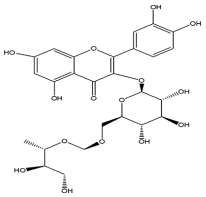
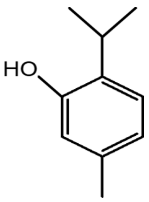
(Contd...)

Table 1: *(Continued)*

S. No.	Ligand	Structure	Binding Energy (kcal/moL)
			Aldose reductase (PDB: 3s3g)
14.	Gymnenic acid		+37.07
15.	Kaempferol		–8.51
16.	Koenidine		**–7.70**
17.	Luteolin-7-glucoside		–7.19
18.	Marmelosin		–6.99
19.	Marmesin		**–9.67**
20.	Naringenin		–8.32

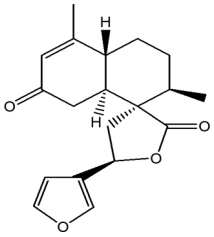
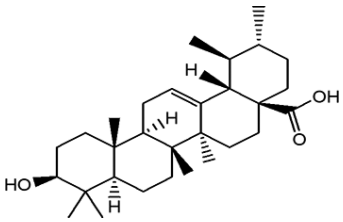
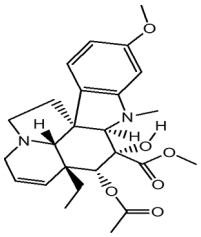
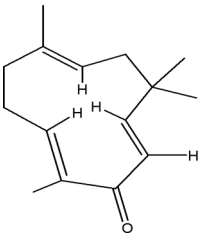
(Contd...)

Table 1: *(Continued)*

S. No.	Ligand	Structure	Binding Energy (kcal/moL)
			Aldose reductase (PDB: 3s3g)
21.	Nicotinic Acid		–5.67
22.	Piperine		**–9.90**
23.	Quercetin		**–8.78**
24.	Quercetrin		–6.70
25.	Rutin2		–5.01
26.	Rutin		–3.74
27.	Thymol		–6.74

(Contd...)

Table 1: *(Continued)*

S. No.	Ligand	Structure	Binding Energy (kcal/moL)
			Aldose reductase (PDB: 3s3g)
28.	Trans-dehydrocrotonin		**–8.24**
29.	Ursolic acid		–3.58
30.	Vindoline		–3.62
31.	Zerumbone		–6.48

In molecular docking studies, a binding energy of ≤ -7 kcal/mol is considered good and having strong therapeutic potential as a drug candidate.

catalytically important residues of AR. Among the screened compounds, 31 ligands exhibited favorable binding energies and stable interaction profiles and were therefore shortlisted for detailed analysis.

Aegelin, piperine, quercetin, apigenin, chrysin, and marmesin were among the phytoconstituents that showed substantial binding affinities. Their docking scores ranged from roughly −8.0 to −10.0 kcal/mol, which were either better than or equal to those of the reference ligand. These substances established important contacts with active-site residues that are known to be essential for the catalytic activity of AR, including Tyr48, His110, Trp111, Trp219, and Leu300. The enzyme's active pocket has hydrophobic contacts and hydrogen bonds, which point to a persistent ligand–receptor complex and possible inhibitory function. While the other ligands from the original 85-compound library demonstrated relatively weaker binding and were disqualified from additional investigation, Table 1 summarizes the binding energies and interaction residues of the 31 shortlisted ligands. The difference between the total number of ligands synthesized and the number shown in the results table is resolved by this explanation.

In vitro antidiabetic evaluation

AR inhibitory activity

At different dosages ranging from 100 to 700 µg/mL, the phytoconstituents Aegelin, Quercetin, Piperine, Apigenin, and Chrysin were tested for their ability to inhibit AR enzyme activity. Aegelin, quercetin, piperine, apigenin, and chrysin all showed maximal inhibitions of 87.18, 86.67, 86.33, 85.77, and 81.13%, respectively. Aegelin, quercetin, piperine, apigenin, and chrysin were shown to have IC_{50} values of 5.96, 5.89, 5.77, 5.08, and 3.96 µg/mL [Figure 2].

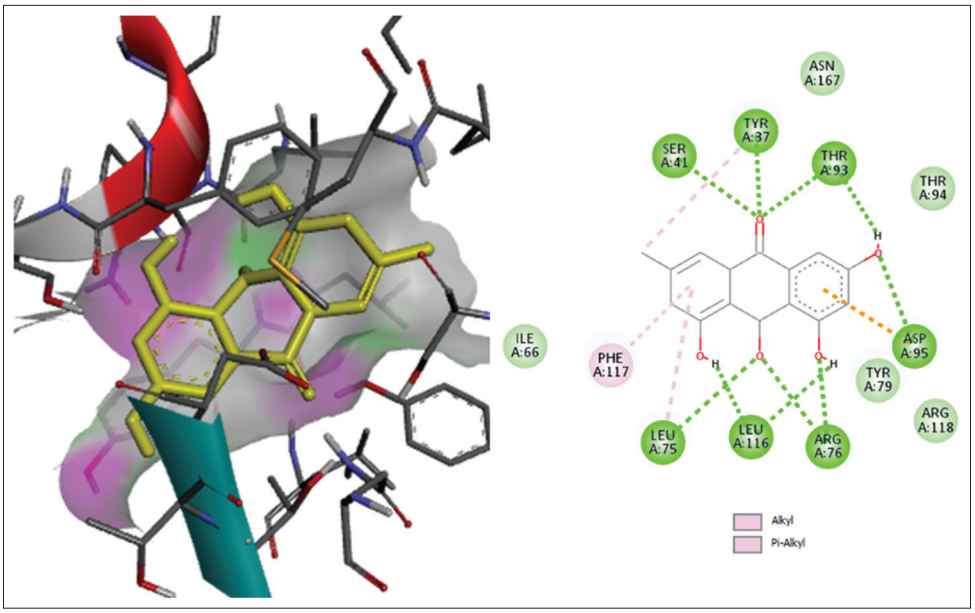


Figure 1: Two-dimensional and three-dimensional binding interactions of emodin with human aldose reductase (PDB ID: 3S3G), shown as a representative ligand to illustrate the general binding mode within the enzyme active site

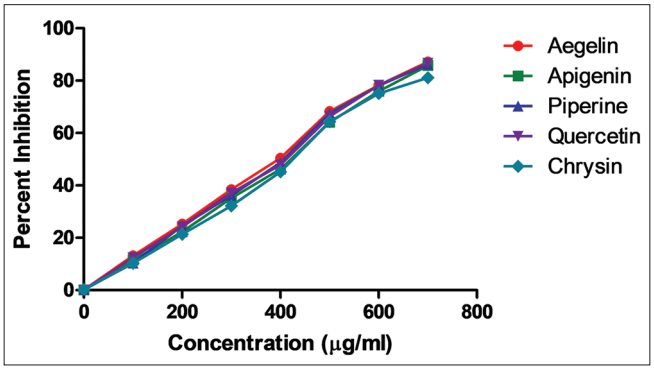


Figure 2: Aldose reductase inhibitory activity of aegelin, apigenin, piperine, quercetin and chrysin

In diabetes mellitus, the balance of carbohydrate and lipid metabolism is disrupted due to impairments in either insulin production or its action. It is a significant non-communicable metabolic disorder associated with substantial healthcare expenses and a high mortality rate. Phytoconstituents are vital in managing diabetes mellitus, especially through their impact on glucose metabolism, which is frequently disrupted in diabetic individuals. These organic substances offer a more secure, all-encompassing, and cost-effective substitute for diabetes treatment and prevention. Controlling blood glucose levels after meals is crucial for those with diabetes, especially those with type 2 diabetes mellitus. An essential digestive enzyme called α-amylase helps break down complex carbs like starch into simpler sugars like glucose. Excess glucose in diabetes is redirected into an alternate metabolic pathway known as the polyol pathway, especially when blood glucose regulation is poor. Within this pathway, the enzyme AR plays a crucial role by converting glucose into sorbitol, a type of sugar alcohol. Later, this sorbitol accumulates in the cells of various organs such as retina, kidney, and nerves responsible for diabetic complications. Hence, ARIs are viewed as a potential approach for managing chronic diabetic complications, particularly in individuals with inadequate glycemic control or early signs of organ damage. Natural agents targeting this enzyme are currently the focus of extensive research and clinical investigation. In the present study, we have evaluated five phytoconstituents for AR enzyme inhibition. The dose-dependent inhibition of AR, as well as optimum IC_{50} values of phytoconstituents points us to towards the development of better therapeutic agent as compare to synthetic chemicals.

CONCLUSION

The study results demonstrate that molecular docking–based selection of these phytoconstituents supports their binding affinity and interaction with key active sites of the target enzymes, thereby reinforcing their therapeutic potential. The tested phytoconstituents exhibited notable inhibitory effects on AR enzymes. Such enzyme inhibition may represent one of the mechanisms underlying their role in the management or prevention of type 2 diabetes. These observations indicate that the phytoconstituents hold promise as potential candidates for developing novel oral hypoglycemic agents. Overall, the findings highlight a rational approach combining experimental assays and molecular docking to identify promising lead compounds for Type 2 diabetes management.

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