



MORINGA OLEIFERA ISOTHIOCYANATE: AN IN SILICO APPROACH AGAINST ALDOSE REDUCTASE

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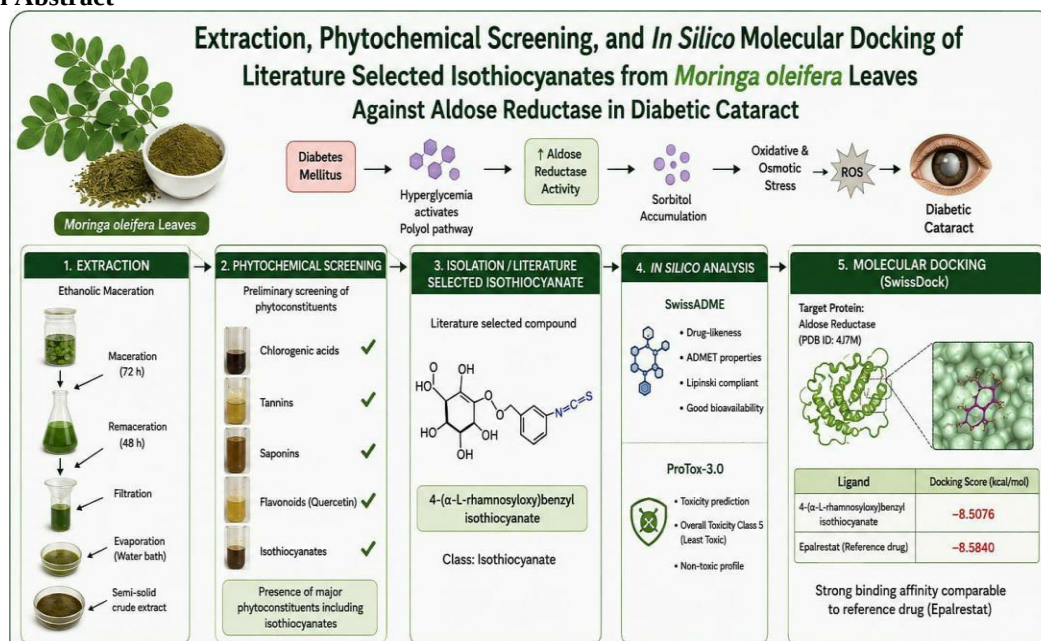
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ABSTRACT

Diabetic cataract is a major ocular complication of diabetes mellitus, in which persistent hyperglycemia promotes the polyol pathway and enhances the activity of aldose reductase, leading to oxidative and osmotic stress in the lens. The present study aimed to investigate literature-selected isothiocyanates from *Moringa oleifera* leaves as potential aldose reductase inhibitors using an integrated experimental and in silico approach. *Moringa oleifera* leaves were collected, shade-dried, powdered, and subjected to ethanolic maceration followed by remaceration to obtain the crude extract. Preliminary phytochemical screening was performed to identify the major classes of phytoconstituents present in the extract, with particular emphasis on isothiocyanates. A literature-based isothiocyanate, 4-(α -L-rhamnosyloxy)benzyl isothiocyanate, was selected for further computational evaluation. The physicochemical and pharmacokinetic properties of the selected compound were assessed using SwissADME, while toxicity prediction was performed using ProTox-3.0. Molecular docking was subsequently carried out against aldose reductase to evaluate the binding potential and interaction profile of the selected isothiocyanate. The selected compound exhibited a predicted docking score of -8.5076 kcal/mol, which was comparable to the reference aldose reductase inhibitor epalrestat (-8.5840 kcal/mol). The docking analysis indicated favorable interactions of the ligand within the active-site region of aldose reductase. Overall, the findings suggest that 4-(α -L-rhamnosyloxy) benzyl isothiocyanate from *Moringa oleifera* may possess potential as a lead compound for aldose reductase inhibition. However, further in vitro enzyme inhibition studies and in vivo investigations are required to validate the observed computational findings and establish its therapeutic potential against diabetic cataract.

KEYWORDS: *Moringa oleifera*; Isothiocyanates; Aldose reductase; Diabetic cataract; in silico study.

Graphical Abstract



INTRODUCTION

Medicinal plants have been considered as important sources of biologically active compounds with high therapeutic values and have been used extensively in traditional systems of medicine in the prevention and management of different diseases. The different medicinal plants, *Moringa oleifera* Lam., which is commonly referred to as the drumstick tree or the miracle tree, is a member of the Moringaceae family and is grown in tropical and subtropical parts of the world, including India. The plant has been considered to be a very important medicinal plant due to the presence of unique pharmacological activities besides being a source of nutrition. Most of the parts of the plant, including leaves, seeds, flowers, pods, bark, and roots, have been used in traditional medicine for the treatment of different diseases, including diabetes, inflammation, microbial infections, hypertension, anemia, and oxidative stress.

The leaves of *Moringa oleifera* contain high concentrations of nutrients such as proteins, vitamins (A, C, and E), minerals (calcium, potassium, and iron), dietary fibers, and an array of secondary metabolites. The phytochemicals in this tree are comprised of flavonoids, phenolic acids, tannins, saponins, alkaloids, glucosinolates, and isothiocyanates. This combination makes the tree exhibit impressive biological activities. Of these phytochemicals, isothiocyanates have been highly researched for their strong antioxidants, anti-inflammatory, antidiabetic, antimicrobial, and chemoprotective activities. These compounds help protect cells against oxidative stress by scavenging free radicals and regulating various cellular signaling pathways involved in disease progression.

In recent years, numerous pharmacological studies have demonstrated that *Moringa oleifera* leaf extracts possess

significant antioxidant and antihyperglycemic activities, making them promising candidates for the management of diabetes and its associated complications. The antioxidant properties of the plant help reduce oxidative damage caused by excessive reactive oxygen species, while its antidiabetic effects contribute to improved glucose metabolism and reduced tissue injury. Since oxidative stress and activation of the polyol pathway play major roles in the development of diabetic cataract, the bioactive constituents of *Moringa oleifera*, particularly isothiocyanates, may serve as potential natural inhibitors of disease progression. Therefore, *Moringa oleifera* has emerged as an important medicinal plant for phytochemical investigations and computational drug discovery studies aimed at identifying novel therapeutic agents against diabetic cataract.

Isothiocyanates are a class of naturally occurring phytochemicals that contain sulfur and are mainly formed via the enzymatic hydrolysis reaction of glucosinolates using the enzyme myrosinase. Isothiocyanates are found in abundance in cruciferous vegetables and are also available in the leaves of *Moringa oleifera*. The distinctive chemical nature of isothiocyanates along with their diverse biological actions has gained them much interest in drug discovery and biomedical studies. Isothiocyanates are considered valuable bioactive components owing to their capability to influence several molecular pathways related to chronic diseases.

It has been well established through extensive scientific studies that isothiocyanates have effective antioxidant, anti-inflammatory, antimicrobial, anticancer, antidiabetic, cardioprotective, and neuroprotective effects. The antioxidant property of isothiocyanates plays a role in neutralizing ROS and decreasing oxidative

stress, thus offering protection to the cellular components including proteins, lipids, and DNA against oxidative injury. Moreover, the pharmacological actions of isothiocyanates also include regulation of inflammatory pathways by reducing the production of pro-inflammatory cytokines and mediators.

In the disease called diabetes mellitus, constant hyperglycemia leads to the generation of oxidative stress, inflammation, and activation of the polyol pathway, and thereby causes tissue damage and the formation of complications in diabetes, such as diabetic cataract. The rate limiting enzyme in the polyol pathway is called aldose reductase; this enzyme causes conversion of extra glucose to sorbitol. Sorbitol overproduction causes lens damage through osmotic imbalance, protein precipitation, oxidative stress, and finally opacification of the lens resulting in the formation of cataracts. Hence, inhibition of aldose reductase is an effective treatment for preventing diabetic cataracts. Phytochemicals that can act as inhibitors of aldose reductase are of great importance due to their relative safety and fewer adverse effects than synthetic inhibitors.

Recent pharmacological and computational studies indicate that selected isothiocyanates have the potential to interact with proteins involved in glucose metabolism, oxidative stress, and inflammatory pathways. Their favorable physicochemical characteristics and ability to bind with disease-related targets make them promising candidates for computer-aided drug discovery. Molecular docking is an effective in silico technique that predicts the binding affinity, binding orientation, and molecular

interactions between a ligand and a target protein. This approach helps identify compounds with potential inhibitory activity before conducting laboratory-based biological studies, thereby reducing both time and cost in the drug discovery process.

In the current study, certain isothiocyanates which have been identified from *Moringa oleifera* leaves in previous literature research works have been considered for docking studies on the enzyme aldose reductase to assess the interaction and inhibition capacity. The result of this study can be an important step toward understanding the potential of natural isothiocyanates as aldose reductase inhibitors and the possible development of such isothiocyanates as therapeutics agents for the prevention and management of diabetic cataract.

PLANT PROFILE COMMON NAMES

- Drumstick tree
- Miracle tree
- Horseradish tree
- Ben oil tree
- Sahjan (Hindi)
- Murungai (Tamil)

SCIENTIFIC NAME: *Moringa oleifera* Lam.

FAMILY: Moringaceae.

PART USED: Leaves



Fig. 1: *Moringa oleifera*.

GEOGRAPHICAL SOURCE

Native-India, also widely distributed in tropical and subtropical countries of the world.

Andhra Pradesh, Assam, Gujarat, Karnataka, Kerala, Madhya Pradesh, Tamil Nadu, Nepal, Pakistan, Sri Lanka etc.

REGIONAL NAMES (Botanical description)

Unani - Sahajan

English	-	Horse radish tree, Drumstick tree
Sanskrit	-	Subhanjana
Gujarati	-	Suragavo
Malayalam	-	Murinna, Sigr
Punjabi	-	Sainjna, Soanjna
Ayurvedic	-	Haritashaaka, Raktaka
Arabian	-	Rawag
Latin	-	<i>Moringa oleifera</i>
Tamil	-	Morigkai

Telugu - Mulaga, Munaga
 French - Morungue
 Spanish - Ben, Moringa
 Chinese - La Ken

TAXONOMICAL CLASSIFICATION

Kingdom - Plantae
 Sub kingdom - Tracheobionta

Super Division - Spermatophyta
 Division - Magnoliophyta
 Class - Magnoliopsida
 Subclass - Dilleniidae
 Order - Capparales
 Family - Moringaceae
 Genus - Moringa
 Species - Oleifera



Fig. 2: *Moringa oleifera* leaves.

PHYTOCHEMICAL CONSTITUTE

The plant contains a wide Variety of phytochemical;

- Alkaloids
- Flavonoids
- Saponins
- Tannins
- Glucosinolates
- Glucomoringin
- Isothiocyanates
- Benzyl isothiocyanates
- Phenolic acids (chlorogenic acid, gallic acid, ellagic acid)

MACROSCOPIC CHARACTER OF LEAVES

Color: Fresh leaves are bright to dark green on the upper surface and lighter green on the lower surface; dried leaves are greenish-brown.

Leaf type : Odd-pinnately compound leaves, generally tripinnate.

Leaflets : About 4 to 6 pairs of leaflets per pinna.

Shape : Leaflets are typically ovate, obovate or elliptical.

Size : Approximately 1-2 cm long, 0.5-1cm width.

Base & Apex: Base – Symmetrical to rounded.

Apex – Mucronate or slightly emarginated.

Odour : Characteristic

Taste : Slightly bitter.

MICROSCOPIC CHARACTER

Epidermis : Single-layered upper and lower epidermis covered by a thin cuticle.

Stomato : Usually paracytic (rubaceous) or Anomocytic type.

Trichomes : Unicellular, non-glandular trichomes are typically present on the margins and sometimes along the veins.

Calcium oxalate crystals are present.

Midrib region: Transverse section of midrib reveals a prominent, biconvex structure with a collateral vascular bundle surrounded by a parenchymatous.

Mesophyll : The leaf is dorsiventral, one layer of elongated palisade parenchyma beneath the upper epidermis.

TRADITIONAL USES

Leaves

The leaves are consumed as a nutritious vegetable and are used to manage malnutrition, anemia, general weakness, purgative, piles, fever, malaria, thphoid fever, skin disease and sore throat, hypertension, inflammation, arthritis; leaf juice is control glucose levels.

Root

Used to kidney stones, rheumatism, and joint pain, lower back or kidney pain, constipation, relieve earache, toothache, and inflammatory conditions.

Bark

Used to treat fever, cough, and respiratory ailments, digestive disorders, inflammation, and infectious diseases, to destroy tumor, heal ulcer.

Flower

Flowers are used to produce aphrodisiac substance and to treat inflammation, muscle disease, hysteria, tumors and enlargement of the spleen.

Seed

Used to decreasing liver lipid peroxidase, antihypertensive, diabetes, digestive disorder.

AIM AND OBJECTIVE**AIM**

To investigate the therapeutic potential of selected isothiocyanates from *Moringa oleifera* leaves against diabetic cataract through phytochemical analysis, and in silico molecular docking.

OBJECTIVE

- To collect, authenticate, and prepare the leaves of *Moringa oleifera* for experimental studies.
- To extract the phytoconstituents from *Moringa oleifera* leaves using a suitable solvent extraction method.
- To perform preliminary phytochemical screening for the qualitative identification of major classes of secondary metabolites such as alkaloids, flavonoids, tannins, saponins, glycosides, phenolic compounds, and isothiocyanates.
- To identify and select bioactive isothiocyanates reported from *Moringa oleifera* for computational analysis.
- To prepare the selected ligand molecules and the target protein for molecular docking studies using suitable bioinformatics tools.
- To evaluate the binding affinity, molecular interactions, and docking poses of the selected isothiocyanates with the target protein.



Fig. 3: Dried leaves of moringa oleifera Lam.

Process of extraction

Extraction was carried out by method.

1. MACERATION METHOD**Maceration**

Twenty grams (20 g) of powdered *Moringa oleifera* leaves were accurately weighed and transferred into a clean, dry conical flask. The powdered material was subjected to maceration using ethanol as the extraction solvent. The flask was properly covered and kept at room temperature for 72 hours (3 days) with occasional shaking to facilitate the extraction of phytoconstituents.

- To compare the docking results and identify the compound exhibiting the most favorable protein–ligand interaction.
- To correlate the phytochemical, TLC, and molecular docking findings in order to assess the therapeutic potential of selected isothiocyanates from *Moringa oleifera* leaves.

MATERIAL AND METHODS**Collection of plant**

Sample of *moringa oleifera* Lam was collected in the village from Salem; Tamil Nadu collection was carried out during the early morning hours to ensure freshness and avoid damage due to heat. Healthy and mature plants were carefully identified with the help of local people and traditional knowledge.

Drying and Grinding Process

Fresh, green and healthy leaves are selected. Yellow, damaged, diseased and foreign materials are removed. The leaves are washed thoroughly with clean water to remove dust and other impurities.

After washing, excess surface water is removed by draining the leaves within 7 days at room temperature, under shade, avoiding direct leaves were checked for complete removal of moisture and then ground into a coarse powder using a suitable grinder.

The powdered material was stored in clean, dry, airtight containers at room temperature until further extraction.



Fig. 4: Dried leaves powder.

After 72 hours, the mixture was filtered and the filtrate was collected. The remaining marc was subjected to remaceration with fresh ethanol for 2 days under similar conditions. After 2 days, the mixture was filtered and the second filtrate was collected. Both filtrates were combined and concentrated using a water bath to remove the solvent and obtain the crude extract. The concentrated extract was collected in a clean, dry container and stored appropriately for further phytochemical screening.



Fig. 5: maceration process.



Fig. 6: extraction marc.

Evaporation technique

After completion of extraction, the solvent present in the extraction was removed by evaporation. The extract was first filtered and then concentrated using a suitable evaporation technique such as evaporation on a water bath at controlled temperature to avoid degradation of active constituents. The solvent was allowed to evaporate slowly until a thick, semisolid mass was obtained. After filtration, we obtained 5ml of the product.

Extraction method selection

We performed aqueous extraction by maceration method process. Since the maceration method gave a low yield, it was for further phytochemical screening and activity. Therefore, the maceration extract was used.

Preliminary phytochemical screening

Preliminary phytochemical screening was carried out to find the presence of the active chemical constituents in extra such as alkaloids, glycoside, steroid, flavonoids, Tannis, Glycoside, carbohydrates, amino acid, terpenoids, saponins, fat and oils.

Test for Alkaloids

1. Dragen reagent: 2ml + 1ml dragen reagent = orange reddish brown precipitate present.

2. Mayers test: 1ml extraction + 2 drops of Mayers reagent = White precipitate present.

Test for Tannins

Ferric chloride test: Few drops of 5% ferric chloride solution 2ml of test solution = blue colour present.

Test for saponins

Foam test: 5ml of test solution + shake will 5 minutes in test tube = formation of stable foam.

Test for triterpenoids

Salkowski test: 2mg of dry extract shake with 1ml of chloroform and few drops concentration sulfuric acid reddish colour.

Test for carbohydrate

Molish's test: 1ml test solution + 1% alpha naphthol + 2ml concentration sulfuric acid. = purple ring formed.

Test for phenols

2ml extraction + few drops ferric chloride solution = yellow colour.

Grote's reagent test for (Isothiocyanate's): 2ml extraction + add pinch of sodium bicarbonate and 0.5ml of grote's reagent. = yellowish colour precipitate present.



Fig. 7: phytochemical screening identification test.

MOLECULAR DOCKING STUDY

Molecular docking is a computational method, which is applied to determine the most favorable pose and interaction of a small molecule ligand inside the binding site of the target protein. It is one of the key structure-based approaches of drug discovery, which is utilized to study the potential interactions of proteins and ligands and evaluate their relative binding affinity. Molecular docking algorithms usually consist of multiple steps such as generation of various poses of ligands inside the target binding site and evaluation of generated poses by means of scoring functions. Thus, molecular docking could be applied as a computational tool for the identifying and evaluating of bioactive compounds before further experimental investigation.

Molecular docking can also help to reduce the time and resources required during the initial screening of potential bioactive compounds by prioritizing promising ligands for further experimental evaluation. Thus, it serves as a useful preliminary computational tool in drug discovery and can accelerate the identification of potential protein–ligand interactions. That can be used in drug development processes.

In the present study, molecular docking was performed to investigate the binding potential of a literature-selected isothiocyanate from *Moringa oleifera* leaves against aldose reductase, a target associated with diabetic cataract.

DIABETIC CATARACT (disease)

Cataract is still the first or second cause of blindness in all parts of the world. Cataract does not only occur at a 3–5 times higher rate than in the non-diabetic individuals

but occurs at an early age in the diabetic population. Diabetic cataract is one form of cataract that occurs in relation to diabetes mellitus where the crystalline lens starts to become opacity or cloudy due to a gradual increase in opacity of the previously clear lens. Hyperglycemia can cause some biochemical changes to occur within the lens. These changes include activation of polyol pathway, oxidative stress, osmotic disturbance and non-enzymatic glycation of lens protein.

One of the important biochemical pathways implicated in diabetic cataract formation is the polyol pathway. Under hyperglycaemic conditions, excess glucose is converted to sorbitol by the enzyme aldose reductase using NADPH as a cofactor. Increased aldose reductase activity can therefore lead to enhanced sorbitol formation and accumulation in lens cells.

Sorbitol is less permeable through cell membranes, and its increased levels may lead to osmotic stress and damage to cells. The increased metabolism through the polyol pathway may also lead to oxidative stress and decrease in the antioxidant defense systems, leading to damage to lens proteins and lens fibers. This ultimately leads to the formation of cataracts in diabetic patients.

Aldose reductase (AKR1B1) therefore represents an important molecular target in studies investigating the prevention or management of diabetic cataract. Inhibition of aldose reductase may reduce the conversion of glucose to sorbitol and potentially limit the biochemical changes associated with diabetic lens damage. Based on this role, aldose reductase was selected as the target protein for the present molecular docking study.

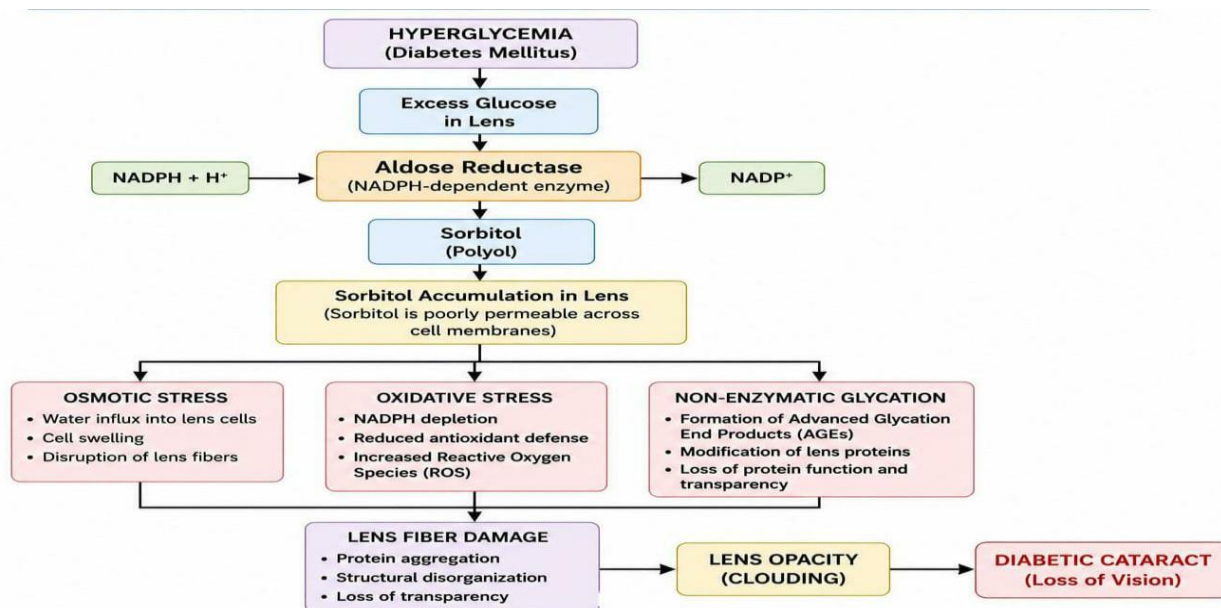


Fig. 8: Polyol pathway in diabetic cataract.

Hyperglycaemia → Glucose → Aldose reductase
 → Sorbitol ↑ → Osmotic/oxidative stress → Lens fibre
 damage → Lens opacity → Diabetic cataract.

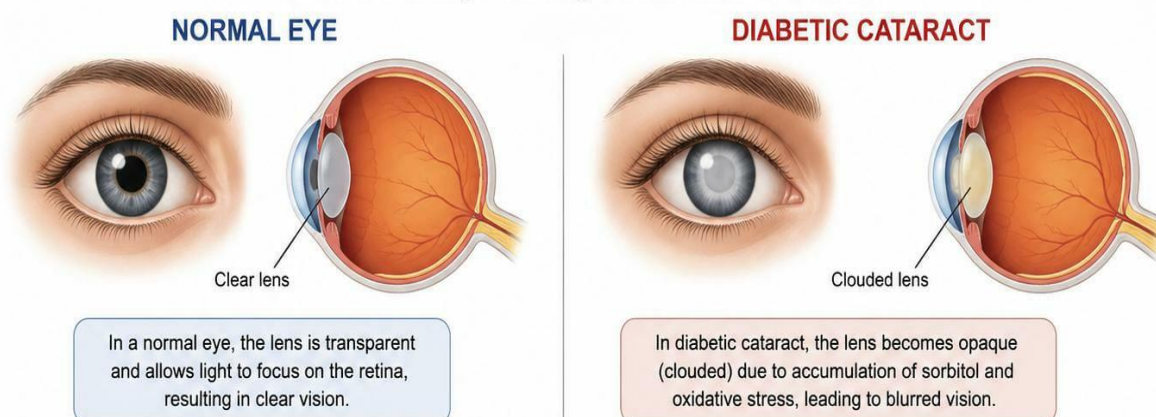


Fig. 9: Schematic Representation of Normal and Diabetic Cataract Eye.

Selection of target protein

[Selected target: Aldose reductase (AKR1B1)]

Aldose reductase (AR/ALR2), also known as aldo-keto reductase family 1 member B1 (AKR1B1), was selected as the target protein for the molecular docking study against diabetic cataract. Aldose reductase is a key enzyme responsible for the conversion of glucose into sorbitol as part of the polyol pathway. The accumulation of sorbitol leads to osmotic and oxidative stress in diabetic conditions, which contributes to the onset and progression of diabetic cataracts. Thus, the inhibition of aldose reductase is believed to be a promising approach

to the prevention or delay of the development of diabetic cataracts. Therefore, inhibition of aldose reductase is considered a potential strategy for preventing or delaying diabetic cataract. For these reasons, aldose reductase was chosen as a target protein.

Preparation

The three-dimensional crystal structure of human aldose reductase was obtained from the Protein Data Bank (PDB). The selected protein structure was used as the receptor for the molecular docking study.

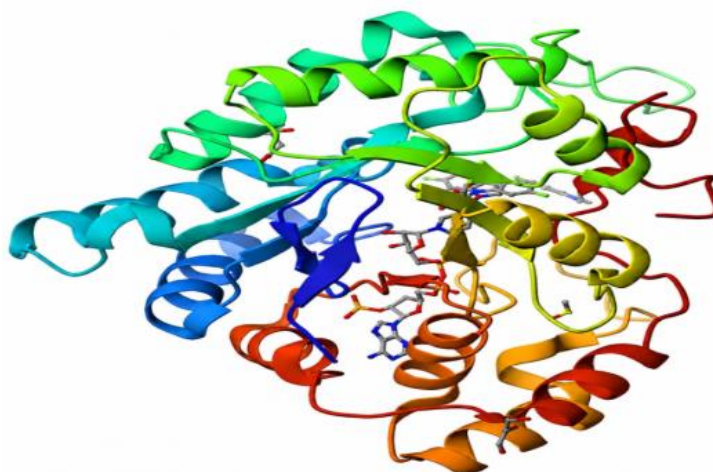


Fig. 10: Three-dimensional structure of aldose reductase (PDB ID: 8BJL).

Parameters

Target protein: Human Aldose reductase
 PDB ID – 8BJL
 Gene/Protein: Aldose reductase (AKR1B1/ALR2)
 Organism: Homo sapiens
 Protein class: Oxidoreductase
 Chain: A
 Method: X-ray diffraction
 Resolution – 0.97 Å

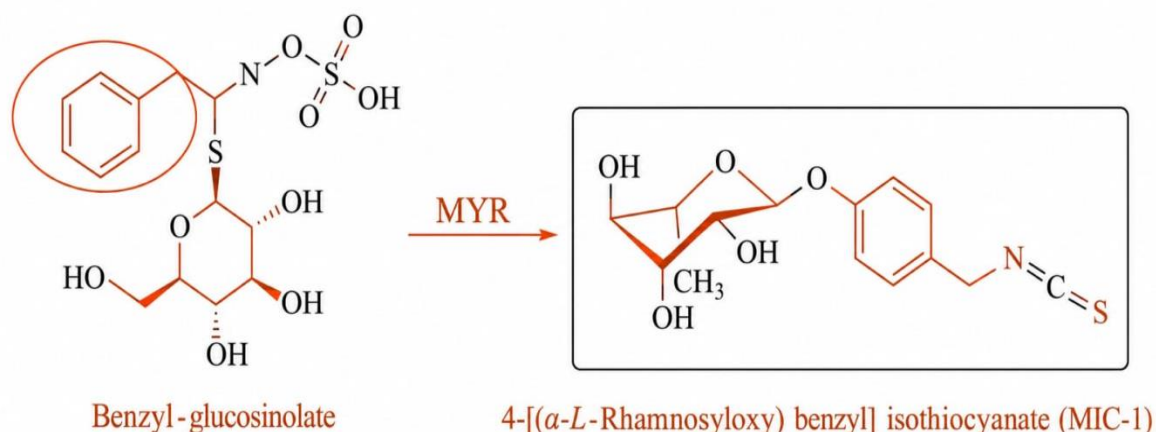
Selection of ligand

[Selected ligand: 4-(α -L-Rhamnosyloxy) benzyl isothiocyanate]

4-[(α -L-rhamnosyloxy)benzyl]isothiocyanate (MIC-1) was selected as the ligand for the present molecular docking study based on its reported occurrence as an isothiocyanate constituent of *Moringa oleifera*. Isothiocyanates are sulfur-containing bioactive compounds ($-N=C=S$) formed from glucosinolates through enzymatic hydrolysis and have been investigated

for their diverse biological activities. These Isothiocyanates have been reported to possess antioxidant and antidiabetic activities, which are relevant

to the pathophysiological mechanisms associated with diabetic complications.



The selected isothiocyanate was considered for the present in silico study to evaluate its potential binding

interaction with human aldose reductase, a target associated with diabetic cataract.

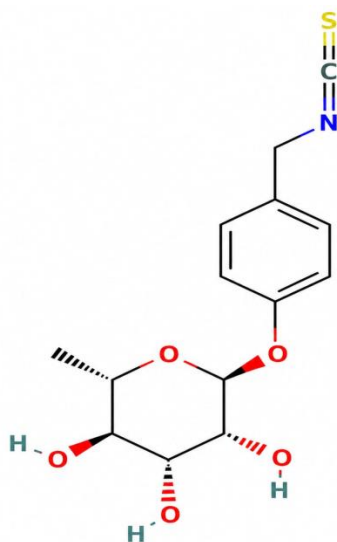


Fig. 11: Two-dimensional chemical structure of 4-(α -L-rhamnosyloxy)benzyl isothiocyanate.

Preparation

The chemical structure of 4-(α -L-rhamnosyloxy) benzyl isothiocyanate was retrieved from the PubChem database using its compound information and canonical SMILES. The ligand structure was obtained in a suitable chemical structure format and prepared for molecular docking.
 SMILES: C[C@H]1[C@@H]([C@H]([C@H]([C@@H]1O)OC2=CC=C(C=C2)CN=C=S)O)O
[Canonical SMILES of 4-(α -L-rhamnosyloxy) benzyl] isothiocyanate obtained from PubChem]

Parameters

Selected ligand: 4-[(α -L-rhamnosyloxy) benzyl]isothiocyanate obtained from PubChem]
 Molecular formula - $C_{14}H_{17}NO_5S$
 Molecular weight - 311.36 g/mol
 PubChem CID: CID153557
 Common name: Moringin / Glucomoringin isothiocyanate (GMG-ITC)

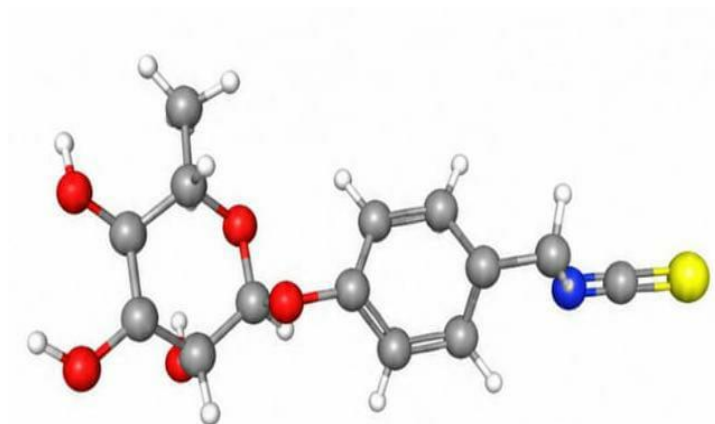


Fig. 13: 3D structure.

Selection of reference/Standard drug

The compound Epalrestat was selected as the reference inhibitor for the molecular docking study because it is a well-established aldose reductase inhibitor. Since aldose reductase (AKR1B1) was selected as the target protein for the present study, epalrestat was selected as the

standard drug to provide a reference for comparison with the binding affinity of the selected isothiocyanate against human aldose reductase (PDB ID: 8BJL). The docking performance of the selected ligand was subsequently compared with that of epalrestat under the docking conditions used in the present study.

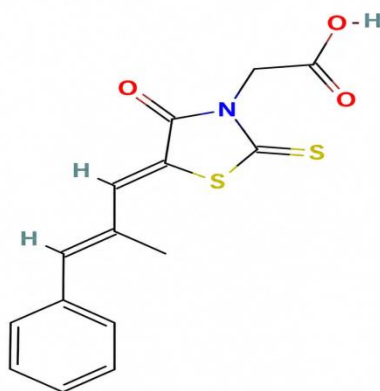


Fig. 14: Two-dimensional chemical structure of Epalrestat.

The structure of the reference compound epalrestat was downloaded from PubChem through its corresponding Compound ID (CID1549120). The canonical SMILES for epalrestat was downloaded and utilized for preparing the ligand. The prepared reference compound was then submitted to the SwissDock web-based platform for docking against the selected aldose reductase target protein.

Molecular formula: C₁₅H₁₃NO₃S₂

Molecular weight: 319.4 g/mol

Canonical SMILES: C/C(=C/C1=CC=CC=C1)/C=C2/C(=O)N(C(=S)S2)CC(=O)O

ADME Prediction

The ADME and drug-likeness parameters of the selected isothiocyanate, 4-[(α -L-rhamnosyloxy) benzyl] isothiocyanate, were determined through prediction using the SwissADME web based tool. Canonical SMILES of the selected ligand were obtained from the chemical database and inputted into the SwissADME tool. Physiochemical, pharmacokinetics, and drug-likeness parameters were determined by using the tool, such as molecular weight, lipophilicity, aqueous solubility, gastrointestinal absorption, blood-brain permeability, topological polar surface area (TPSA), Lipinski's Rule of Five, and bioavailability score. The obtained computational predictions were recorded for further analysis.

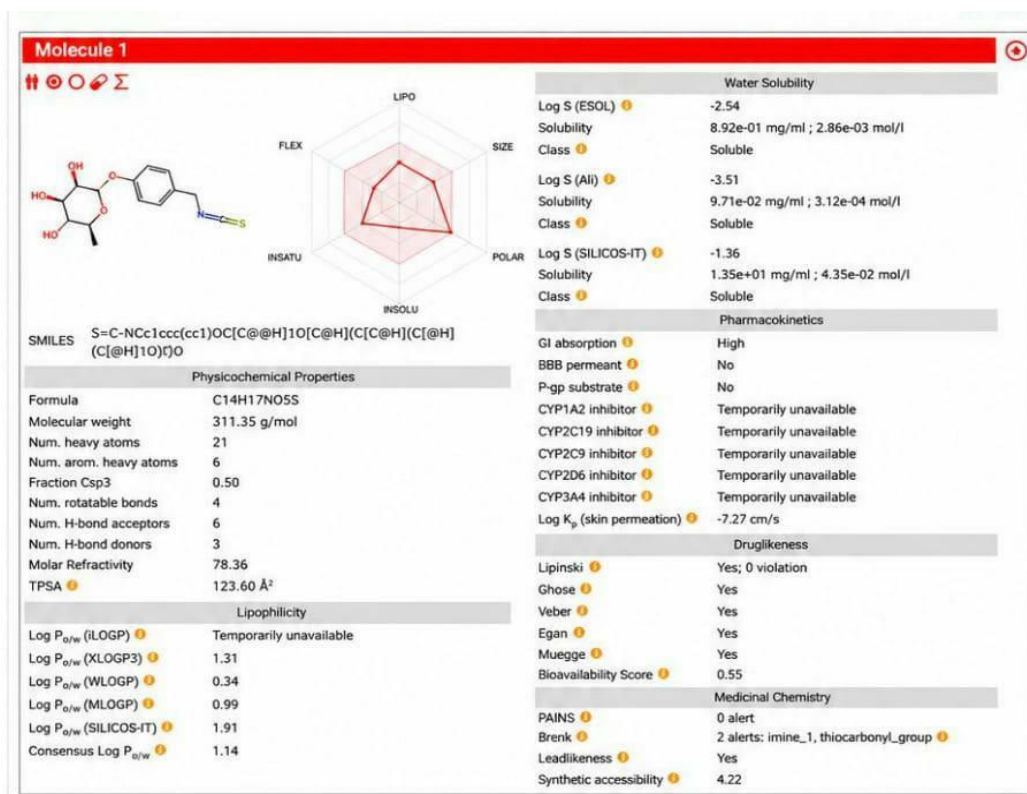


Fig. 15: SwissADME profile of 4-[(α -L-rhamnosyloxy)benzyl]isothiocyanate.

The selected isothiocyanate showed high gastrointestinal absorption and was predicted to be non-permeable to the blood–brain barrier. It showed no violation of Lipinski's rule of five and a predicted bioavailability score of 0.55. These computational findings provide a preliminary assessment of the drug-likeness and pharmacokinetic properties of the selected compound.

Toxicity Prediction

The toxicity profile of the selected ligand, 4-[(α -L-rhamnosyloxy) benzyl]isothiocyanate, was predicted

through the use of the online toxicity prediction tool, ProTox-3.0. The ligand was subjected to testing for its acute oral toxicity as well as selected toxicity end points such as hepatotoxicity, neurotoxicity, nephrotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. The predicted LD₅₀ value, toxicity class, and selected toxicity endpoint predictions were recorded to obtain a preliminary assessment of the toxicological profile of the selected ligand.



making it a Toxicity Class 5 compound. It was predicted to be inactive with regard to hepatotoxicity,

neurotoxicity, carcinogenicity, mutagenicity and cytotoxicity. On the other hand, positive predictions were made with regards to nephrotoxicity, cardiotoxicity and immunotoxicity. These in silico findings provide a preliminary toxicity profile and require further experimental validation.

DOCKING PROCEDURE

Molecular docking was conducted using the SwissDock online docking server to examine the interaction between the selected ligand and the aldose reductase target protein. The 3D model of aldose reductase that was prepared was considered the target protein, whereas 4-(α -L-rhamnosyloxy) benzyl isothiocyanate was the test ligand. Epalrestat was used as the reference ligand for

comparative analysis. The prepared protein and ligand structures were then uploaded into the SwissDock site to start the docking process.

The SwissDock software provided various possible docking poses of the ligand with respect to the target protein. The pose with the most negative binding score was considered the best-ranked pose. The docking results were then ranked based on the predicted binding energy of the poses. The docking pose that was ranked highest was then chosen for further investigation regarding the protein-ligand interaction. The same procedure was followed for Epalrestat, and the obtained docking results were compared with those of the selected ligand.

DOCKING RESULT

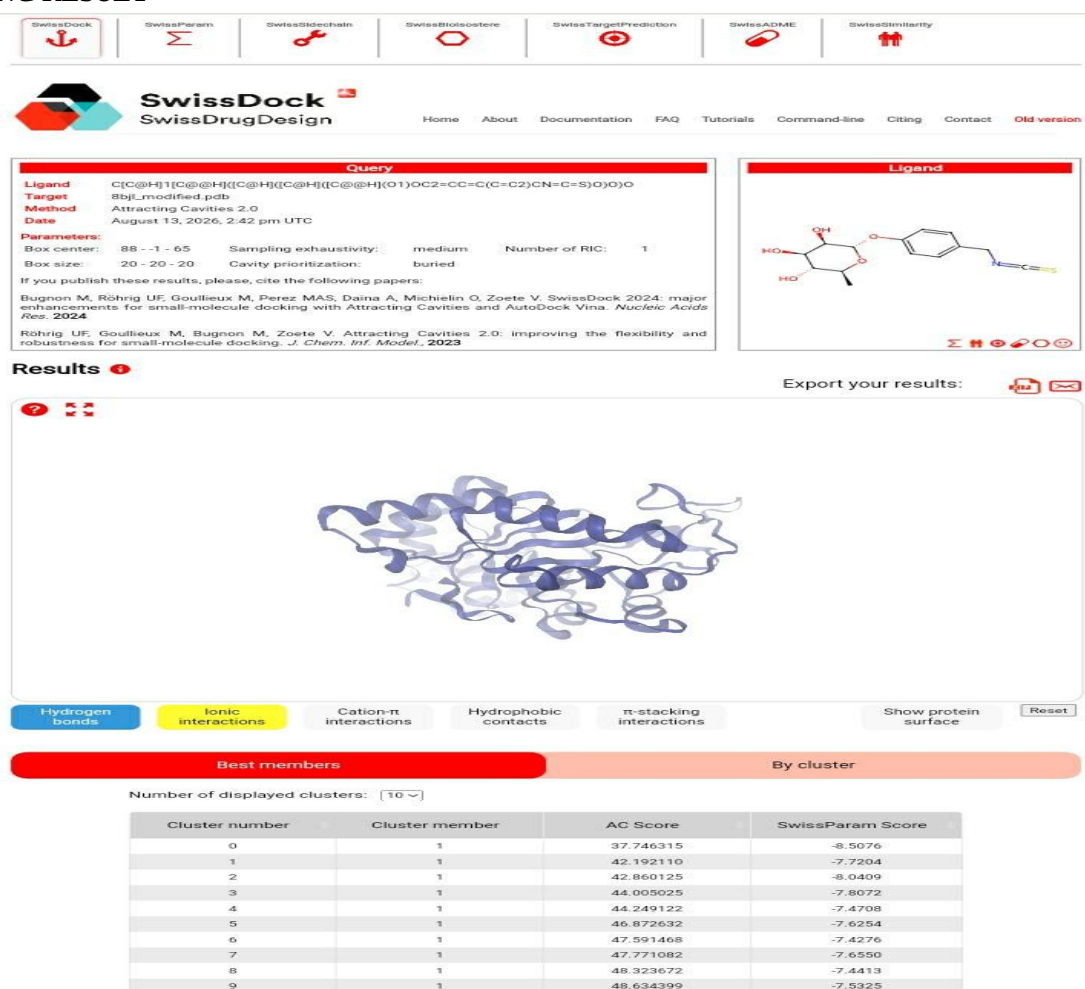


Fig. 18: SwissDock molecular docking result of 4-(α -L-rhamnosyloxy) benzyl isothiocyanate with aldose reductase.

Ligand	4-(α -L-rhamnosyloxy)benzyl isothiocyanate
Target protein	Aldose reductase
Best Cluster	0
SwissParam Score	-8.5076

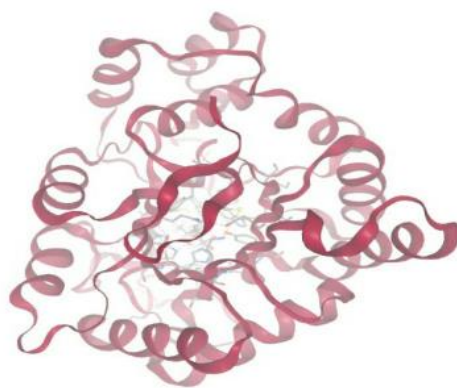


Fig. 19: Three-dimensional visualization of the best-ranked docking pose of 4-[(α -L-rhamnosyloxy) benzyl] isothiocyanate with aldose reductase (PDB ID: 8BJL).

The molecular docking study of the selected 4-(α -L-rhamnosyloxy) benzyl isothiocyanate against aldose reductase was performed using SwissDock. The ligand exhibited a SwissParam Score of -8.5076 in the best-

ranked docking solution. The predicted docking result indicates a favourable binding of the selected phytoconstituent within the binding site of aldose reductase.

Docking Result of the Reference Drug

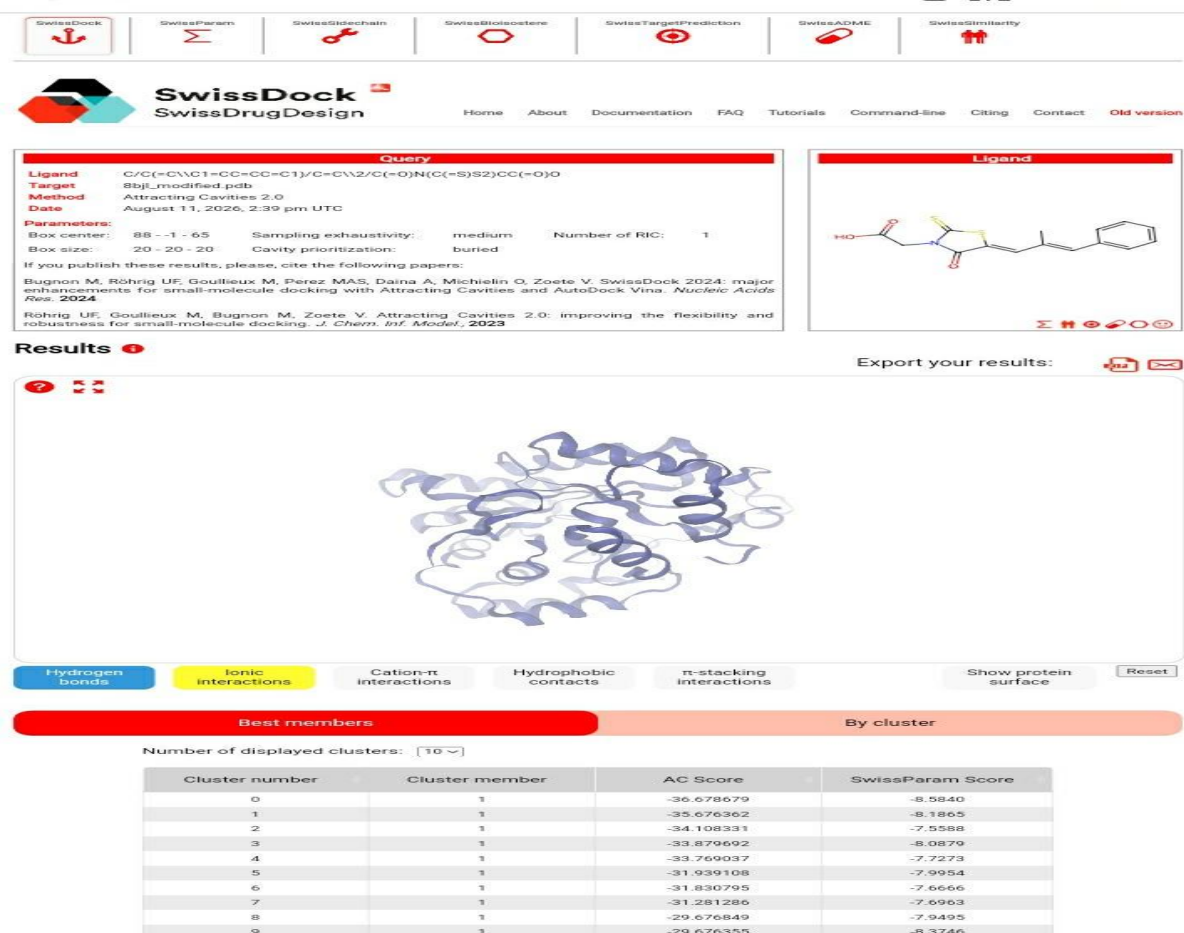


Fig. 20: SwissDock docking result of Epalrestat with aldose reductase.

Epalrestat, a known aldose reductase inhibitor, was used as a reference ligand to provide a benchmark for evaluating the docking performance of the selected

phytoconstituent. Epalrestat showed a SwissParam Score of -8.5840 against aldose reductase.

Docking Score Comparison

Ligand	4-(α -L-rhamnosyloxy)benzyl isothiocyanate	Epalrestat
Role	Selected ligand	Reference drug
Target Protein	Aldose reductase	Aldose reductase
SwissParam Score	-8.5076	-8.5840

The docking activity of the selected compound 4-(α -L-rhamnosyloxy) benzyl isothiocyanate was compared with that of the reference aldose reductase inhibitor called Epalrestat. The selected phytoconstituent had a score of -8.5076 in the SwissParam Docking Score, whereas Epalrestat had a score of -8.5840. The docking score of the selected phytoconstituent was equivalent to that of the standard drug, but the standard drug has a slightly more negative docking score. These findings indicate that the selected phytoconstituent exhibited a favourable predicted interaction with aldose reductase and supports its further investigation as a potential ligand.

The selected 4-(α -L-rhamnosyloxy)benzyl isothiocyanate from *Moringa oleifera* leaves showed a favourable predicted docking score of -8.5076 against aldose reductase, which was comparable to the reference inhibitor Epalrestat (-8.5840).

DISCUSSION

The present study was carried out to investigate the potential of a literature-selected isothiocyanate from *Moringa oleifera* leaves against aldose reductase associated with diabetic cataract. *Moringa oleifera* is a medicinally important plant containing various bioactive phytoconstituents, including flavonoids, phenolic compounds, glucosinolates and isothiocyanates. Isothiocyanates have been reported to possess antioxidant and antidiabetic properties and were therefore considered relevant to the present study.

In the present work, *Moringa oleifera* leaves were extracted using ethanol by maceration followed by remaceration. Preliminary phytochemical screening of the obtained extract showed the presence of different phytoconstituents, including alkaloids, tannins, saponins, triterpenoids, Carbohydrates, phenolic compounds and isothiocyanates. The detection of isothiocyanates supported the consideration of a literature-reported *Moringa oleifera* isothiocyanate for further computational evaluation.

Diabetic cataract is associated with persistent hyperglycaemia and activation of the polyol pathway. Aldose reductase converts excess glucose into sorbitol, and increased sorbitol accumulation contributes to osmotic imbalance, oxidative stress and lens damage. Based on its important role in this pathway, human aldose reductase was selected as the target protein for the molecular docking study.

The selected ligand, 4-(α -L-rhamnosyloxy) benzyl isothiocyanate, was selected based on its reported occurrence in *Moringa oleifera*. The ligand structure was

retrieved from PubChem and prepared for docking. Human aldose reductase with PDB ID: 8BJL was used as the target protein. Epalrestat, a known aldose reductase inhibitor, was used as the reference compound for comparison.

The SwissADME prediction of the selected isothiocyanate showed favourable preliminary drug-likeness characteristics. The compound showed high gastrointestinal absorption, no violation of Lipinski's Rule of Five and a predicted bioavailability score of 0.55. It was also predicted to be non-permeable to the blood-brain barrier. These findings indicate favourable preliminary physicochemical and pharmacokinetic characteristics of the selected compound.

The ProTox-3.0 prediction showed a predicted LD₅₀ value of 3750 mg/kg, corresponding to Toxicity Class 5. The compound was predicted to be inactive for hepatotoxicity, neurotoxicity, carcinogenicity, mutagenicity and cytotoxicity, while positive predictions were obtained for nephrotoxicity, cardiotoxicity and immunotoxicity. Thus, the toxicity prediction provided a preliminary computational profile of the selected ligand.

Molecular docking was performed using SwissDock to evaluate the binding potential of the selected isothiocyanate towards aldose reductase. The selected compound showed a SwissParam Score of -8.5076, indicating a favourable predicted binding interaction with the target protein. In comparison, the reference drug Epalrestat showed a SwissParam Score of -8.5840. The docking score of the selected isothiocyanate was therefore close to that of Epalrestat, although Epalrestat showed a slightly more negative score.

Overall, the present findings indicate that 4-(α -L-rhamnosyloxy) benzyl isothiocyanate possesses favourable predicted binding towards aldose reductase along with acceptable preliminary drug-likeness characteristics. The docking result comparable to the reference inhibitor supports the potential of this *Moringa oleifera* isothiocyanate as a promising candidate for further investigation against diabetic cataract.

CONCLUSION

The present study investigated the potential of a literature-selected isothiocyanate from *Moringa oleifera* leaves against aldose reductase, an important enzyme involved in the polyol pathway associated with diabetic cataract. Preliminary phytochemical screening of the *Moringa oleifera* leaf extract indicated the presence of several bioactive phytoconstituent classes, including isothiocyanates. The literature-selected compound 4-(α -

L-rhamnosyloxy) benzyl isothiocyanate was subsequently evaluated using computational approaches.

The selected isothiocyanate showed favourable preliminary ADME characteristics, including high gastrointestinal absorption and no violation of Lipinski's Rule of Five. Toxicity prediction indicated a predicted LD₅₀ of 3750 mg/kg and Toxicity Class 5, although some toxicity endpoints require further experimental confirmation.

Molecular docking against human aldose reductase (PDB ID: 8BJL) produced a SwissParam Score of -8.5076 for 4-(α -L-rhamnosyloxy) benzyl isothiocyanate, while the reference aldose reductase inhibitor Epalrestat produced a score of -8.5840. The selected isothiocyanate therefore demonstrated a favourable predicted binding score that was comparable to the reference drug, although Epalrestat showed a slightly more negative score.

Thus, the findings of the present study suggest that 4-(α -L-rhamnosyloxy) benzyl isothiocyanate from *Moringa oleifera* may have potential as a lead compound targeting aldose reductase in diabetic cataract. The study provides a preliminary computational basis for further investigation of this natural isothiocyanate. However, the findings are predictive in nature and should be confirmed through aldose reductase enzyme inhibition assays, in vitro studies, toxicity evaluation and suitable in vivo investigations before considering its therapeutic application.

Further experimental studies, including in vitro and in vivo investigations, are necessary to confirm its aldose reductase inhibitory activity, safety, and potential usefulness in the management of diabetic cataract.

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