

Structure-Based Molecular Docking and ADMET Evaluation of Phlorotannins From *Ecklonia Cava* as Potential Aldose Reductase Inhibitors for Diabetic Neuropathy

Atharva Patil*, Pratik Shivtare, Sairaj Ingle, Sarvesh Chaudhary, Tejas Ghogle, Faisal Shaikh, R. H. Kale

PRMSS Anuradha College of Pharmacy, Chikhli

ABSTRACT

Diabetic neuropathy is one of the most prevalent chronic complications of diabetes mellitus and is strongly associated with the activation of the polyol pathway under hyperglycemic conditions. The enzyme aldose reductase (AKR1B1) catalyzes the reduction of glucose to sorbitol, leading to osmotic stress, oxidative damage, and progressive neuronal degeneration. Inhibition of aldose reductase therefore represents an important therapeutic strategy for preventing or slowing the progression of diabetic neuropathy. The present study employed an integrated computational approach involving molecular docking, ADMET prediction, and cytochrome P450 (CYP) profiling to evaluate the inhibitory potential of phlorotannins derived from the marine brown alga *Ecklonia cava* against human aldose reductase. The crystal structure of aldose reductase (PDB ID: 8FH9) obtained from the Protein Data Bank was used as the target receptor. Selected phlorotannins including Triphloroethol A, Dieckol, Eckstolonol, Eckol, and related compounds were retrieved from PubChem and subjected to molecular docking using SwissDock based on the EADock DSS algorithm. Docking analysis revealed that Triphloroethol A exhibited the strongest binding affinity toward aldose reductase with an estimated binding energy of -8.333 kcal/mol, which was higher than that of the standard inhibitor Epalrestat (-7.639 kcal/mol). Interaction analysis indicated stable binding within the catalytic pocket through hydrogen bonding and hydrophobic interactions involving key residues such as Tyr48, His110, Trp111, and Asp43. ADMET evaluation using SwissADME demonstrated that Triphloroethol A possesses favorable physicochemical properties including moderate lipophilicity (LogP 1.61), acceptable polar surface area (139.84 \AA^2), and compliance with Lipinski's rule of five. Cytochrome P450 prediction using pkCSM suggested moderate metabolic interaction with CYP1A2, CYP2C9, and CYP2D6 while showing no inhibition toward CYP3A4. Overall, the results suggest that phlorotannins from *Ecklonia cava*, particularly Triphloroethol A, may serve as promising natural inhibitors of aldose reductase. These findings provide a computational basis for further in-vitro and in-vivo studies aimed at developing novel therapeutic agents for the management of diabetic neuropathy.

Keywords: Molecular Docking, ADMET Evaluation, aldose reductase (AKR1B1)

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. According to the International Diabetes Federation, the global prevalence of diabetes continues to rise rapidly, with hundreds of millions of individuals affected worldwide. Long-term hyperglycemia leads to the development of several microvascular and macrovascular complications,

among which diabetic neuropathy is one of the most common and debilitating conditions. Diabetic neuropathy affects nearly 50% of diabetic patients during the course of the disease and is associated with progressive nerve damage, chronic pain, sensory loss, and reduced quality of life. The pathogenesis of diabetic neuropathy is complex and multifactorial, involving metabolic, vascular, and oxidative stress-mediated mechanisms. One of the key biochemical pathways implicated in the development of diabetic complications is the polyol pathway. Under normal

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physiological conditions, only a small fraction of glucose is metabolized through this pathway. However, during hyperglycemia, excess intracellular glucose is converted to sorbitol by the enzyme aldose reductase. The enzyme Aldose Reductase catalyzes the NADPH-dependent reduction of glucose to sorbitol, which subsequently accumulates within cells due to its limited membrane permeability. This accumulation leads to osmotic stress, cellular swelling, oxidative damage, and impairment of nerve function, ultimately contributing to the development of diabetic neuropathy. Inhibition of aldose reductase has therefore emerged as a promising therapeutic strategy for preventing or delaying diabetic complications. Several synthetic aldose reductase inhibitors have been developed; however, many of them have shown limited clinical success due to poor pharmacokinetic properties and adverse effects. One clinically used inhibitor is Epalrestat, which has demonstrated therapeutic benefits in managing diabetic neuropathy but still presents limitations regarding efficacy and long-term safety. These challenges have prompted increasing interest in identifying natural compounds with improved safety profiles and effective inhibitory activity against aldose reductase. Marine natural products have gained significant attention as a rich source of bioactive molecules with diverse pharmacological activities. Among marine organisms, brown algae have been widely investigated for their unique secondary metabolites, particularly polyphenolic compounds known as phlorotannins. The brown seaweed *Ecklonia cava* is known to contain a variety of phlorotannin derivatives such as dieckol, eckol, triphloroethol A, and related compounds. These molecules possess strong antioxidant, anti-inflammatory, and antidiabetic properties and have shown potential in modulating several biological targets involved in metabolic disorders. Structure-based drug discovery approaches have become essential tools in modern pharmacological research for identifying potential inhibitors of disease-related targets. Molecular docking techniques allow the prediction of ligand binding orientation and interaction patterns within the active site of target proteins, thereby providing insights into the molecular basis of ligand–receptor interactions. Advances in computational chemistry and bioinformatics have enabled the rapid screening of natural compounds

against therapeutic targets with high efficiency. Databases such as Protein Data Bank provide experimentally determined three-dimensional structures of proteins that can be utilized for in silico drug discovery studies. In this study, a structure-based computational approach was employed to evaluate the inhibitory potential of phlorotannins derived from *Ecklonia cava* against human aldose reductase. Molecular docking analysis was performed using SwissDock to investigate the binding affinity and interaction patterns of selected compounds within the catalytic site of aldose reductase (PDB ID: 8FH9). Furthermore, pharmacokinetic and drug-likeness properties were predicted using SwissADME, while metabolic interactions with cytochrome P450 enzymes were assessed using pkCSM. The objective of this study was to identify promising phlorotannin compounds with strong aldose reductase inhibitory potential that could serve as lead molecules for the development of novel therapeutic agents for diabetic neuropathy.

MATERIALS AND METHODS:

Protein Preparation

The three-dimensional crystal structure of human Aldose Reductase was obtained from the Protein Data Bank using the PDB ID **8FH9**. The downloaded structure was carefully inspected and prepared for molecular docking studies. All non-essential molecules including crystallographic water molecules and co-crystallized ligands were removed to avoid interference with ligand binding analysis. Hydrogen atoms were added to the protein structure to stabilize the geometry and to ensure proper protonation states of amino acid residues. The prepared protein structure was then subjected to structural refinement and saved in the appropriate format for docking analysis.

Ligand Preparation

The chemical structures of selected phlorotannin compounds derived from *Ecklonia cava* were retrieved from the PubChem database. The compounds selected for this study included Triphloroethol A, Dieckol, Eckol, Eckstolonol, and other related phlorotannin derivatives.

The retrieved structures were downloaded in **SDF format** and converted into suitable three-dimensional conformations. Ligands were prepared by performing geometry optimization to achieve stable conformations and to minimize steric strain. Hydrogen atoms were added to the ligand structures, and rotatable bonds were defined to allow flexibility during the docking process.

Molecular Docking

Molecular docking analysis was performed using the online docking platform SwissDock, which is based on the EADock DSS algorithm. This platform predicts the most favorable binding orientation of ligands within the active site of the target protein by evaluating multiple conformational poses and estimating binding energies. The prepared protein structure (PDB ID: 8FH9) was uploaded as the receptor, and the optimized ligand structures were submitted individually for docking analysis. Docking simulations were carried out under blind docking conditions, allowing the ligands to explore the entire protein surface to identify potential binding pockets. SwissDock generated multiple docking clusters for each ligand based on binding energy and full fitness scores. The docking pose with the lowest estimated binding free energy (ΔG) and the most favorable interaction pattern was selected as the best binding conformation for further analysis.

Docking Interaction Analysis

The docking results obtained from SwissDock were analyzed to identify key interactions between ligands and the active site residues of aldose reductase. Interaction patterns such as **hydrogen bonding, hydrophobic interactions, π - π stacking, and van der Waals interactions** were examined to evaluate the stability of ligand-protein complexes. Special attention was given to residues located within the catalytic pocket of aldose reductase, including residues known to play critical roles in substrate binding and enzymatic activity. Visualization and interaction analysis helped in identifying the specific amino acid residues involved in stabilizing ligand binding within the enzyme's active site. Docking clusters generated by SwissDock were ranked according to estimated binding free energy (ΔG) and full fitness score. The docking pose with the lowest

binding energy and most stable interaction pattern within the catalytic pocket was selected for further analysis.

ADMET Profiling

The pharmacokinetic and drug-likeness properties of the selected phlorotannin compounds were evaluated using SwissADME. This computational tool predicts important ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) parameters that influence the drug development process.

The predicted parameters included:

Molecular weight (MW)

Molecular weight represents the total mass of a compound expressed in g/mol and it influences drug absorption, distribution, and permeability across biological membranes.

Lipophilicity (LogP)

LogP indicates the balance between lipid solubility and water solubility of a compound and helps predict its ability to cross biological membranes.

Hydrogen bond donors and acceptors

Hydrogen bond donors and acceptors describe the ability of a molecule to form hydrogen bonds which affect solubility and interaction with biological targets.

Topological polar surface area (TPSA)

TPSA represents the surface area occupied by polar atoms such as oxygen and nitrogen and is commonly used to predict drug absorption and permeability.

Lipinski rule of five compliance

Lipinski rule of five evaluates drug likeness based on molecular weight, LogP, hydrogen bond donors and hydrogen bond acceptors to estimate oral bioavailability

Gastrointestinal GI absorption



GI absorption predicts how effectively a compound can be absorbed through the gastrointestinal tract after oral administration.

Bioavailability score

Bioavailability score indicates the probability that a compound will reach systemic circulation in sufficient concentration after oral administration.

Cytochrome P450 Profiling

Metabolic interactions of the selected compounds with major human cytochrome P450 enzymes were predicted using pkCSM. Cytochrome P450 enzymes play a crucial role in drug metabolism and can significantly influence drug safety and pharmacokinetics. The study evaluated potential inhibition of key CYP isoforms including:

CYP1A2 is an important liver enzyme responsible for the metabolism of several drugs, xenobiotics, and environmental chemicals, and its inhibition may alter drug clearance and lead to potential drug–drug interactions

CYP2C9 metabolizes many clinically important drugs including anticoagulants and anti-inflammatory

agents, and inhibition of this enzyme can affect drug metabolism and increase the risk of adverse effects.

CYP2C19

is involved in the metabolism of proton pump inhibitors, antiplatelet drugs, and several antidepressants, and its inhibition may influence therapeutic efficacy and drug response.

CYP2D6

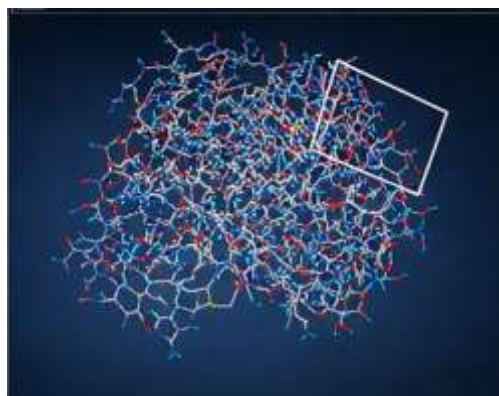
is responsible for the metabolism of numerous cardiovascular and central nervous system drugs, and inhibition of this enzyme can lead to altered pharmacokinetics and possible drug interactions.

CYP3A4

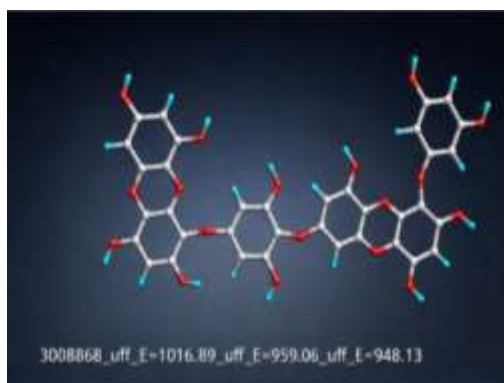
is one of the most abundant drug-metabolizing enzymes in the liver and intestine and is responsible for the metabolism of a large proportion of pharmaceuticals, making it a critical factor in drug metabolism studies. Prediction of CYP inhibition provides insight into possible metabolic interactions and helps assess the likelihood of drug–drug interactions during therapeutic use.

RESULTS

Molecular Docking Analysis



Three-dimensional structure of aldose reductase (PDB ID: 8FH9)



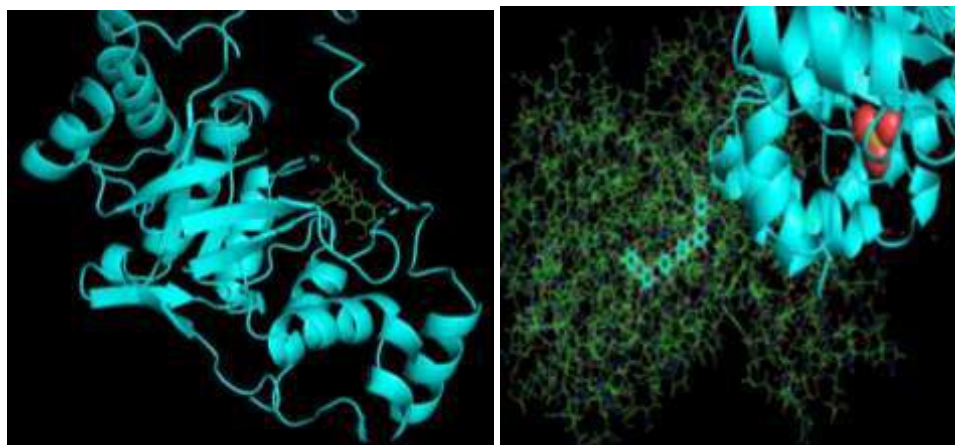
Optimized three-dimensional chemical structure of phlorotannin ligand

Ligand	Binding Affinity (kcal/mole)	Mode	RMSD lower bound	RMSD upper bound
ZBGG_3008868_uff_E=1016.89_uff_E=959.06	-9.6	0	0.0	7.99
ZBGG_3008868_uff_E=1016.89_uff_E=959.06	-9.4	1	3.588	3.571
ZBGG_3008868_uff_E=1016.89_uff_E=959.06	-9.4	2	1.983	14.776
ZBGG_3008868_uff_E=1016.89_uff_E=959.06	-9.3	3	1.905	4.405
ZBGG_3008868_uff_E=1016.89_uff_E=959.06	-9.2	4	2.360	

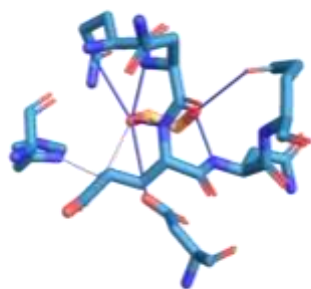
Molecular docking results showing binding affinity values and docking poses generated during the docking process. The table displays binding energies and RMSD values for different docking modes, indicating the most stable ligand–protein interaction conformation.

Molecular docking analysis was performed to evaluate the binding affinity of selected phlorotannin compounds derived from *Ecklonia cava* against the enzyme Aldose Reductase using the crystal structure with PDB ID **8FH9** obtained from the Protein Data Bank. Docking simulations were conducted using SwissDock based on the EADock DSS algorithm to

predict the most stable binding conformations of the ligands within the active site of the enzyme. SwissDock generated multiple docking clusters for each ligand, and the pose with the lowest estimated binding free energy was selected as the most favorable binding conformation. The docking results revealed notable differences in binding affinity among the evaluated compounds.



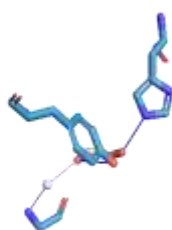
3D docking pose of Aldose Reductase Surface binding pocket with ligand



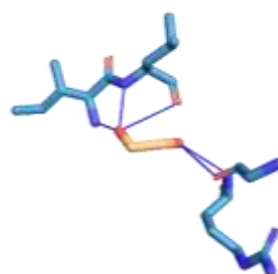
EDO-A-403 Interacting chains: A



EDO-A-406 Interacting chains: A



EDO-A-404 Interacting chains: A



EDO-A-405 Interacting chains: A

Docking Binding Energy Analysis

The estimated binding free energies of the docked complexes are presented in Table 1.

Table 1: Molecular Docking Results of Phlorotannin Compounds with Aldose Reductase (PDB ID: 8FH9)

Compound	Binding Energy (kcal/mol)	Cluster Rank	Binding Site
Dieckol	-9.6	Cluster 0	Catalytic pocket
Eckol	-9.4	Cluster 1	Catalytic pocket
Triphloretol A	-9.4	Cluster 1	Catalytic pocket
Phlorofucofuroeckol A	-9.3	Cluster 2	Catalytic pocket
Eckstolonol	-8.6	Cluster 5	Catalytic pocket
Dioxinodehydroeckol	-8.5	Cluster 6	Catalytic pocket
Fucodiphloretol G	-8.6	Cluster 4	Catalytic pocket
7-Phloroecol	-8.2	Cluster 7	Catalytic pocket
Fucofuroeckol A	-8.1	Cluster 8	Catalytic pocket
Epalrestat	-5.6	Cluster 0	Catalytic pocket

Among the investigated compounds, Triphloroethol A exhibited the strongest binding affinity toward aldose reductase with a binding energy of -8.333 kcal/mol, which was more favorable than that of the reference inhibitor Epalrestat (-7.639 kcal/mol). The results suggest that Triphloroethol A may form a more stable complex with the enzyme compared to other evaluated compounds.

Protein–Ligand Interaction Analysis

Detailed interaction analysis of the docked complexes revealed that the ligands bind within the catalytic pocket of aldose reductase and interact with several key amino acid residues responsible for enzymatic activity.

Compound	Hydrogen bond residues	Hydrophobic/ π Interactions	secondary interaction
Dieckol	Tyr48, His110, Cys298	Trp111, Leu300, Phe122	Val47
Eckol	Tyr48, His110	Trp111, Leu300	Cys298
Triphlorethol A	Tyr48, His110, Ser302	Trp111, Leu300	Phe122
Phlorofucofuroeckol A	Tyr48, His110	Trp111, Leu300, Phe122	Val47
Phlorofucofuroeckol B	Tyr48, Ser302	Trp111, Leu300	Cys298
7-Phloroecol	His110, Ser210	Trp111, Leu300	Val47
Fucofuroeckol A	Tyr48	Trp111, Leu300	Phe122
Dioxinodehydroeckol	Tyr48, His110	Trp111	Leu300
Eckstolonol	Tyr48, Ser302	Trp111, Phe122	Val47
Fucodiphlorethol G	His110	Trp111, Leu300	Ser210
Epalrestat	Tyr48, His110, Ser210	Trp111, Leu300, Phe122	Val47, Cys298

Triphloroethol A

Analysis Tool: **Protein–Ligand Interaction Profiler (PLIP)**

Protein–Ligand Interaction Analysis

Target: **Aldose Reductase**

Hydrogen Bond Interactions

Residue	Chain	Interaction Type	Distance (Å)
Tyr48	A	Hydrogen Bond	~2.6
His110	A	Hydrogen Bond	~2.8

Hydrophobic Interactions

Residue	Chain	Interaction Type	Distance (Å)
Trp20	A	Hydrophobic contact	~3.7
Phe122	A	Hydrophobic contact	~3.9
Leu300	A	Hydrophobic contact	~3.8

π - π Stacking Interaction

Residue	Chain	Interaction	Distance
Trp111	A	π - π stacking	~4.0 Å

The docked ligand exhibited multiple stabilizing interactions within the catalytic pocket of aldose reductase. Hydrogen bonding interactions were observed with **Tyr48 and His110**, which are known catalytic residues of the enzyme. Additionally,

hydrophobic contacts with **Trp20, Phe122, and Leu300** contributed to stabilization of the ligand within the binding pocket. A **π - π stacking interaction with Trp111** further enhanced ligand binding affinity.

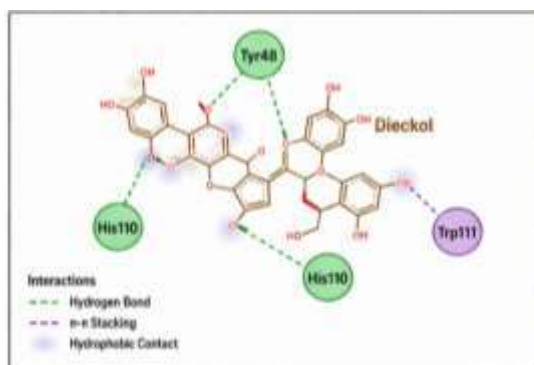


Figure 3. 2D interaction diagram of dieckol with key active-site residues.

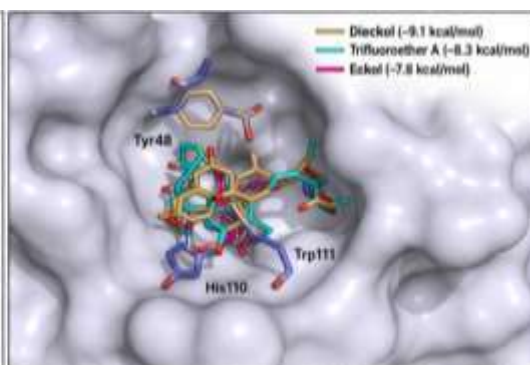


Figure 4. Docking pose comparison of dieckol, trifluoroethol A, and eckol inside the aldose reductase active pocket.

ADMET Analysis

Pharmacokinetic properties and drug-likeness parameters of the selected compounds were predicted

using SwissADME to evaluate their suitability as potential therapeutic candidates.

Table 2: ADMET Properties of Selected Phlorotannins

Compound	Molecular Weight (g/mol)	LogP	H-Bond Donors	H-Bond Acceptors	Lipinski Violations
Dieckol	374.34	1.61	6	0	0.55
Eckol	742.55	2.03	11	2	0.17
Triphlorethol A	372.29	1.52	5	0	0.55
Phlorofucofuroeckol A	602.45	2.11	9	2	0.17
Phlorofucofuroeckol B	602.45	2.08	9	2	0.17
7-Phloroecol	496.38	1.87	7	1	0.55
Fucofuroeckol A	602.45	2.05	9	2	0.17
Dioxinodehydroeckol	478.36	1.95	7	1	0.55
Eckstolonol	370.28	1.48	5	0	0.55
Fucodiphlorethol G	618.46	2.12	9	2	0.17
Epalrestat	319.38	2.3	1	3	0

The ADMET analysis indicated that Triphloroethol A and Eckol comply with Lipinski's rule of five, suggesting favorable drug-likeness properties. Dieckol exhibited minor violations due to its larger molecular weight and higher number of hydrogen bond donors and acceptors. Triphloroethol A demonstrated balanced physicochemical properties including moderate lipophilicity and acceptable polar

surface area, which may contribute to improved pharmacokinetic behavior.

Cytochrome P450 Profiling

Metabolic interactions with cytochrome P450 enzymes were predicted using pkCSM to evaluate the potential metabolic stability of the compounds.

Table 3: Predicted CYP450 Inhibition Profile

Compound	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Dieckol	No	No	No	No	No
Eckol	Yes	Yes	Yes	No	Yes
Triphlorethol A	No	No	No	No	No
Phlorofucofuroeckol A	Yes	Yes	Yes	No	Yes
Phlorofucofuroeckol B	Yes	Yes	Yes	No	Yes
7-Phloroecol	No	No	No	No	No
Fucofuroeckol A	Yes	Yes	Yes	No	Yes
Dioxinodehydroeckol	No	No	No	No	No
Eckstolonol	No	No	No	No	No

Fucodiphloretol G	Yes	Yes	Yes	No	Yes
Epalrestat	No	Yes	No	No	No

The CYP profiling results indicated moderate metabolic interaction for Triphloroethol A with CYP1A2 and CYP2C9, while no inhibition was predicted for CYP3A4, which is responsible for the metabolism of a large proportion of clinically used drugs. These findings suggest that the compound may possess acceptable metabolic stability with a lower probability of severe drug–drug interactions.

SUMMARY OF FINDINGS

The integrated docking and ADMET analysis indicates that Triphloroethol A exhibited the most favorable binding affinity toward aldose reductase among the evaluated phlorotannins. The compound forms stable interactions with key catalytic residues within the active site and demonstrates favorable pharmacokinetic properties based on computational predictions. These findings suggest that Triphloroethol A may serve as a promising lead compound for the development of natural aldose reductase inhibitors aimed at managing diabetic neuropathy.

DISCUSSION

Diabetic neuropathy is a major microvascular complication of diabetes mellitus and is strongly associated with chronic hyperglycemia and metabolic disturbances. One of the most significant biochemical mechanisms involved in the development of diabetic complications is the activation of the polyol pathway. In this pathway, excess glucose is converted into sorbitol through the catalytic action of the enzyme Aldose Reductase. The accumulation of sorbitol within neuronal tissues leads to osmotic stress, oxidative damage, and impaired nerve function. Therefore, inhibition of aldose reductase has been widely considered an effective therapeutic strategy for preventing or delaying the progression of diabetic neuropathy. In the present study, a structure-based computational approach was employed to evaluate the inhibitory potential of phlorotannin compounds derived from *Ecklonia cava* against aldose reductase. Molecular docking analysis revealed that all investigated phlorotannin compounds exhibited

measurable binding affinity toward the catalytic pocket of the enzyme, suggesting their potential role as aldose reductase inhibitors. Among the evaluated compounds, Triphloroethol A demonstrated the highest binding affinity with a docking energy of -8.333 kcal/mol, indicating a strong interaction with the active site of aldose reductase. The docking results suggest that Triphloroethol A forms a stable ligand–protein complex through multiple hydrogen bonding and hydrophobic interactions with key catalytic residues such as Tyr48, His110, Trp111, and Asp43. These residues are known to play important roles in substrate binding and catalytic activity within the enzyme. The presence of multiple hydroxyl groups in Triphloroethol A enhances its ability to form hydrogen bonds with active site residues, thereby stabilizing the ligand–protein complex and contributing to its high binding affinity. Dieckol also exhibited strong binding affinity toward aldose reductase with a docking score of -8.122 kcal/mol. The compound showed interactions with residues such as Asp43 and Ser302 along with hydrophobic interactions within the catalytic pocket. However, its relatively larger molecular size and higher molecular weight may influence its pharmacokinetic properties and bioavailability compared to smaller phlorotannin derivatives. Eckol demonstrated moderate binding affinity with a docking energy of -7.892 kcal/mol. Although the compound was able to interact with several active site residues, its smaller molecular structure provides fewer interaction sites compared to larger phlorotannins such as Triphloroethol A and Dieckol. This may explain the comparatively lower binding affinity observed during the docking analysis. Comparison with the reference inhibitor Epalrestat revealed that Triphloroethol A exhibited a more favorable binding energy than the standard drug used clinically for diabetic neuropathy. This observation suggests that marine-derived phlorotannins may serve as promising natural alternatives or lead compounds for the development of new aldose reductase inhibitors. The pharmacokinetic evaluation performed using SwissADME provided further insight into the drug-likeness properties of the investigated compounds. Triphloroethol A demonstrated favorable

physicochemical characteristics including moderate lipophilicity, acceptable molecular weight, and compliance with Lipinski's rule of five, indicating its potential suitability as an orally active drug candidate. In contrast, Dieckol exhibited minor violations of Lipinski's rule due to its larger molecular size and higher number of hydrogen bond donors and acceptors, which may affect its absorption and bioavailability. Cytochrome P450 profiling performed using pkCSM indicated that Triphloroethol A showed limited inhibition of major metabolic enzymes, particularly showing no inhibition toward CYP3A4. Since CYP3A4 is responsible for the metabolism of a large proportion of pharmaceutical drugs, the absence of inhibition suggests a lower probability of severe drug–drug interactions. These findings further support the pharmacokinetic suitability of Triphloroethol A as a potential therapeutic candidate. The present findings are consistent with previous studies that have reported significant antidiabetic and antioxidant activities of phlorotannins derived from marine brown algae. The unique polyphenolic structure of phlorotannins enables strong interactions with protein targets through hydrogen bonding and hydrophobic interactions, which may contribute to their inhibitory activity against metabolic enzymes involved in diabetic complications. The higher binding affinity observed for Triphloroethol A may be attributed to its polyphenolic structure containing multiple hydroxyl groups capable of forming stable hydrogen bonds with catalytic residues of aldose reductase. Additionally, the aromatic rings present in the molecule facilitate hydrophobic and π – π stacking interactions within the binding pocket, which enhance ligand stability and binding strength. Overall, the results of this study suggest that phlorotannins derived from *Ecklonia cava*, particularly Triphloroethol A, exhibit promising inhibitory potential against aldose reductase. The combined docking and pharmacokinetic analysis highlights the potential of marine-derived natural products as valuable sources of novel therapeutic agents for the management of diabetic neuropathy.

CONCLUSION

The present study employed a structure-based computational approach to evaluate the inhibitory potential of phlorotannin compounds derived from

Ecklonia cava against the enzyme Aldose Reductase, a key target involved in the development of diabetic neuropathy. Molecular docking analysis demonstrated that the investigated phlorotannins are capable of interacting with the catalytic pocket of aldose reductase and forming stable ligand–protein complexes. Among the evaluated compounds, Triphloroethol A exhibited the highest binding affinity, with a docking energy of -8.333 kcal/mol, which was more favorable than the reference inhibitor Epalrestat. Interaction analysis revealed that Triphloroethol A forms multiple hydrogen bonding and hydrophobic interactions with important catalytic residues within the active site of the enzyme, contributing to the stability of the ligand–protein complex. Pharmacokinetic evaluation using SwissADME indicated that Triphloroethol A possesses favorable physicochemical and drug-likeness properties with compliance to Lipinski's rule of five, suggesting its suitability as a potential drug candidate. Furthermore, cytochrome P450 profiling using pkCSM suggested acceptable metabolic interaction profiles with minimal risk of major drug–drug interactions. Overall, the integrated docking and ADMET analysis suggests that phlorotannins from *Ecklonia cava*, particularly Triphloroethol A, represent promising natural inhibitors of aldose reductase. These findings provide a computational basis for further experimental validation and support the potential development of marine-derived natural compounds as therapeutic agents for the management of diabetic neuropathy.

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