IDENTIFICATION OF POTENTIAL INHIBITORS OF HUMAN ALDOSE REDUCTASE FROM NATURAL COMPOUNDS OF VIETNAMESE MEDICINAL PLANTS USING IN SILICO APPROACHES

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Abstract - Aldose reductase is a crucial component of the polyol pathway and catalyzes the NADPH-dependent reduction of glucose to sorbitol. The high activity of Aldose reductase is involved in the development and pathophysiology of diabetes complications. Therefore, this enzyme has been identified as an important target for treatment of these complications. In this study, we performed in silico investigations on natural compounds derived from Vietnamese medicinal plants to identify potential inhibitors of human Aldose reductase. The results showed that out of 307 compounds, 15 compounds were identified as potential Aldose reductase inhibitors with high docking scores and good pharmacokinetics properties. Among them, eight compounds had been proven to inhibit Aldose reductase. The other seven compounds, including Apigenin-7-O-glucuronide, 4′,7-dihydroxy-3′-methoxyflavan, N-feruloylserotonin, N-(p-Coumaroyl) Serotonin, Rosavin, Apigenin-7,4'-dimethyl ether, and Perlolyrine, should be further investigated to develop potential Aldose reductase inhibitors for the treatment of diabetes complications.

Key words - Aldose reductase; diabetic complications; Vietnamese medicinal plants; molecular docking.

1. Introduction

Aldose reductase (AR) is an Aldo-keto reductase superfamily member that participates in the oxidation and reduction reactions in cellular activities such as metabolism, biosynthesis, and detoxification [1]. Aldose reductase usually occurs in the cytoplasm of cells, such as in the kidneys, lens, retinal capillary wall pericytes, and adrenal glands. It is an enzyme that plays a vital role in the conversion of glucose to sorbitol in the polyol pathway. Several studies have shown the association between AR and the pathogenesis of secondary diabetic complications [2]. In addition, recent studies in cell cultures and animal models have shown that AR plays an important role in inflammatory signaling pathways in both hyperglycemic and normoglycemic conditions [3]. Thus, this enzyme has attracted the interest of many researchers due to its possible physiological roles, and AR inhibitors have also been noticed because they appear to be a promising therapeutic target.

Over the years, several AR inhibitors with promising preclinical potential to treat diabetes complications and inflammatory disorders have been developed. However, only Epalrestat has been approved as a therapeutic drug for diabetic neuropathy [4]. Some drugs have been removed from the market due to safety concerns, while others are currently being tested in clinical trials. As a result, it is crucial to develop novel AR inhibitors with better effectiveness and safety profiles [5]. Natural herbs are one of the prospective approaches in the field of AR inhibition due to their lack of toxicity and other undesirable side effects. A wide range of phytochemicals and extracts have been considered effective AR inhibitors *in vitro*. Plant-derived substances such as terpenoids, alkaloids, coumarins, tannins, flavonoids and other phenolic compounds have been shown to significantly inhibit aldose reductase [6].

In addition to *in vitro* and *in vivo* studies, *in silico* method is currently being developed to screen herbal compounds with AR inhibitory effects. This approach has proved valuable in the large-scale screening of various medicinal plants, and it can still be useful to experimentalists by reducing the number of molecules that should be examined *in vitro* conditions [7]. Therefore, this study was designed to investigate the ability to inhibit AR of the phytochemicals present in some Vietnamese medicinal plants. By using computational techniques such as molecular docking and pharmacokinetic and toxicological properties prediction, this investigation identified 15 potential Aldose reductase inhibitors. Out of these, seven compounds have not yet been investigated for their aldose reductase inhibitory activity.

2. Methods

2.1. Protein and ligand preparation

3D structure of the Aldose reductase was downloaded from Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) with accession number 4XZH. The complex 4XZH contains the co-crystallized ligand [3-(4-chloro-3-nitrobenzyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl]acetic acid (ligand 48I), water and cofactor. Before docking the molecule, the protein B-chain, water molecules, and other non-protein molecules were removed. After that, the structure file of Aldose reductase was converted into dockable format (pdpqt) by Protein Preparation tool in EasyDockVina2.2.

According to the referenced research literature, the 3D structures of natural compounds were downloaded from the Pubchem database or drawn by the MarvinSketch tool. All compound files were then converted into dockable format (pdbqt) using Ligand Preparation function in EasyDockVina2.2.

2.2. Molecular docking and interaction analysis

Virtual screening of the compounds was conducted by AutoDock Vina. The center of the grid box was determined

based on the active site of Aldose reductase and the binding site of ligand 48I in the crystal structure. The docking box was determined in a grid box of size 25 Å x 25 Å x 25 Å, with the center site (x,y,z) being (0.5480, 5.0139, -5.1744), respectively.

The interactions between Aldose reductase and compounds were analyzed using "Receptor-Ligand Interactions" tool in Discovery Studio Visualizer 2020 software. The parameters were set at default with main parameters such as max distance for hydrogen bond (3.40 Å), max distance for electrostatic interaction (5.60 Å), max distance for hydrophobic interaction (6.00 Å).

2.3. Pharmacokinetic and toxicological properties prediction

The pharmacokinetic and toxicological properties of compounds were predicted using the admerSAR tool (http://lmmd.ecust.edu.cn/admetsar2/). Based on these predicted properties**,** the ADMET-score of compounds was calculated and used to assess their chemical drug-likeness [8]. This ADMET-score was constructed based on 18 ADMET features, and the ADMET-score of DrugBank was utilized as threshold to select potential candidates.

3. Results and discussion

The list of 30 Vietnamese medicinal plants was selected based on their popularity and applicability. Among these, several plants are commonly used as spices, such as ginger (*Zingiber officinale*), turmeric (*Curcuma longa*) and rosemary (*Rosmarinus officinalis*). Several other plants have been widely used in Vietnamese traditional medicine, such as artichoke (*Cynara scolymus*), *Cleistocalyx operculatus*, moringa (*Moringa oleifera*), stinking passion-flower (*Passiflora foetida*), and *Eurycoma longifolia*,… These plant species have all been demonstrated to have various effects, including antioxidant properties, anti-inflammatory activity, liver detoxification, and anti-diabetic effects [9], [10], [11], [12], [13]. After studying the literature, we collected data of 307 natural compounds from 30 medicinal plants. A library of 3D structures of these compounds was created using Pubchem and MarvinSketch for virtual screening.

To evaluate the docking process, the co-crystallized ligand was isolated from the 4XZH complex and then re-docked to the active site of AR to evaluate the difference in conformation and orientation in docking results compared to the co-crystallization position of that ligand. The docking process is considered reliable if the root-mean-square deviation (RMSD) value between the ligand's re-docking pose and crystal poses is less than 2Å [14]. After re-docking the co-crystalline ligand, the results showed an RMSD value of 1.69Å < 2Å, indicating that this docking protocol is reliable. In addition, the ligand 48I in the AR crystal structure is also a potent inhibitor with an IC50 value of 25 nM [15]. Thus, ligand 48I was used as a reference during the screening process to evaluate the AR inhibitory properties of compounds. When docking between AR and 48I ligand, we recorded a binding energy of -9.4 (kcal/mol). Therefore, we took the threshold to determine the docking result of a compound is -9.9 kcal/mol.

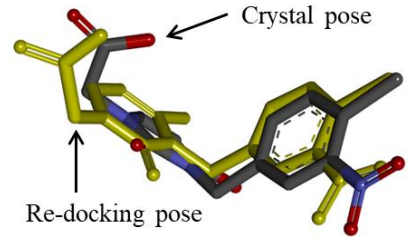


Figure 1. *Re-dock results of co-crystallized ligand 48I*

After docking 307 natural compounds from 30 medicinal plants into AR, the result showed 15 compounds surpassed this threshold (Table 1). Baicalin and Methyl 3.5-di-O-caffeoyl quinate exhibited the best binding affinity (-11.1 kcal/mol); the other compounds had an affinity in the range of -9.9 to -11.0 kcal/mol. All top hit compounds would be subjected to an in silico ADMET analysis to evaluate their pharmacokinetic and toxicological properties.

Table 1. *Top natural compounds with good docking results*

No	Compound	Affinity (kcal/mol)	ADMET-score
1	Baicalin	-11.1	0.752
2	Methyl 3,5-di-O-caffeoyl quinate	-11.1	0.724
3	Apigenin-7-O-glucuronide	-11.0	0.836
4	N-feruloylserotonin	-10.7	0.633
5	4′,7-dihydroxy-3′-methoxyflavan	-10.7	0.729
6	N-(p-Coumaroyl) Serotonin	-10.7	0.676
7	Rosmarinic acid	-10.4	0.797
8	Curcumin	-10.4	0.520
9	Isochlorogenic acid A	-10.3	0.783
10	Verbascoside	-10.3	0.778
11	Cynaroside	-10.3	0.750
12	Isochlorogenic acid B	-10.1	0.724
13	Rosavin	-10.1	0.621
14	Apigenin-7,4'-dimethyl ether	-9.9	0.555
15	Perlolyrine	-9.9	0.647

In drug discovery and development, chemical absorption, distribution, metabolism, excretion, and toxicity play critical roles. Candidate compounds with high in vitro efficacy at a specific target and good ADMET characteristics are preferred in the current drug discovery process. Since ADMET has many features, we used ADMET score calculation of Longfei Guan to simplify the analysis process [8]. In their study, Longfei Guan and colleagues calculated the ADMET-score based on the weights and transformed values of 18 pharmacokinetic and toxicological properties. To select the potential compounds with good pharmacokinetic and toxicological properties, the ADMET-score threshold chosen here is 0.5037, which is the same as the average ADMET score value of the FDA-approved drugs from DrugBank [8]. The results show that all compounds have ADMET-score better than 0.5037. In which Apigenin-7-O-glucuronide had the highest value of 0.836, while Curcumin had the lowest ADMET-score of 0.520. Based on the ADMET-score, the ADMET properties of all potential compounds are similar to the FDA-approved drugs from DrugBank.

It is worth noting that when we reviewed the publications on these compounds, we found that more than half of these compounds (8/15) had already demonstrated their in vitro inhibitory activity against AR. They include Curcumin [16], Methyl 3,5-di-O-caffeoyl quinate [17], Cynaroside [18], Rosmarinic acid [19], Baicalin [20], Isochlorogenic acid A [21], Isochlorogenic acid B [21], and Verbascoside [22]. This indicates that these virtual screening results are highly reliable. In addition, the other seven compounds with good docking scores and drug-likeness properties could be promising AR inhibitors, so they should have further investigation.

Table 2. *Interactions between AR and potential compounds*

Compound	Interactions			
	Total	H-bonds	Hydrophobic interactions	II-sulfur interactions
Apigenin-7-O-glucuronide	11	6	4	1
4′,7-dihydroxy-3′-methoxyflavan	17	2	13	2
Apigenin-7,4'-dimethyl ether	17	10	6	1
N-feruloyl serotonin	14	6	8	0
N-(p-Coumaroyl) Serotonin	12	6	6	0
Rosavin	18	15	3	0
Perlolyrine	14	5	7	2

Among these seven potential compounds, the flavonoids group accounts for the majority with three compounds, including Apigenin-7-O-glucuronide, Apigenin-7,4'-dimethyl ether, 4',7-dihydroxy-3'-methoxyflavan. Flavonoids are one of the most characteristic compounds found in plants. While flavonoids have little nutrient benefit, they have various pharmacological effects, including antioxidative and AR characteristics. Several studies have shown that numerous flavonoids have significant AR inhibitory activity *in vitro* and *in vivo* [6] Quercetin, a flavonoid, was shown to inhibit human Aldose reductase with IC_{50} of 5 μM [23], or rutin, a bioflavonoid, suppressed AR with an IC_{50} value of 13 μM [24], indicating its potential as a preventive or therapeutic agent for diabetes complications. In addition to flavonoids, three compounds belonging to the alkaloid category were identified. They are N-feruloylserotonin, N-(p-Coumaroyl) serotonin, and Perlolyrine. In previous studies, some alkaloids like berberine, palmatine, and coptisine, have demonstrated the ability to inhibit AR activity [25]. However, these alkaloids are isoquinoline and bis-isoquinoline alkaloids, which differ significantly from N-feruloylserotonin and N-(p-Coumaroyl) serotonin, as the latter two contain a serotonin moiety in their structures. Meanwhile, Perlolyrine belongs to another group of alkaloids that is characterized by a β-Carboline ring. Rhetsinine is another alkaloid that has been shown to effectively suppress AR. This indole alkaloid is derived from a hot water extract of *Evodia rutaecarpa* and can inhibit AR with IC_{50} = 24.1 μM [26].

For an in-depth assessment of Aldose reductase inhibition, these 7 compounds were analyzed in more detail for their interactions at the active site of AR using the BIOVIA Discovery Studio 2020 tool. The results in Table 2 indicated that all compounds interacted with AR through interactions including hydrogen bonding, hydrophobic interactions, and π-sulfur interactions. Among these, Rosavin had the most interactions, with 18 interactions.

According to studies of the structure and catalysis mechanism of Aldose Reductase, several amino acid residues in the active site play a critical role in the catalytic activity of AR. These amino acids can be divided into an anion-binding recognition region and a hydrophobic region. The first group consists of Asp43, Tyr48, Lys77, His110, Ser159, Asn160, Gln183, and Tyr209, with the nicotinamide coenzyme linked to these residues via a dense network of hydrogen bonds. Within these amino acids, Tyr48 acts like a proton donor to the carbonyl oxygen atom of the substrate, while His110 keeps the substrate in the active site in the correct orientation [3]. This site allows different substrates and inhibitors to attach anionic or hydrogen-bonded acceptor groups or both. The second group includes Trp20, Trp79, Trp111, Phe122, Pro218, Trp219, Cys298, and Leu300. This hydrophobic region contains a "specificity" pocket including Trp111, Thr113, Phe122, Ala299, Leu300, Ser302, and Cys303 and exhibits considerable flexibility in comparison to the anion-binding region [27]. Compounds that interact with these critical amino acids may interfere with the role of those amino acids in the function of AR. Therefore, these compounds will have a high probability of inhibiting the activity of AR. Interaction analysis revealed all 7 compounds interacted with these key amino acids:

– 4′,7-dihydroxy-3′-methoxyflavan interacted with Trp20, Trp111, Thr113, Tyr209, Trp219, Cys298, Leu300, Cys303.

– Apigenin-7,4'-dimethyl ether interacted with Trp20, Tyr48, His110, Trp111, Gln183, Tyr209, Cys298.

– Apigenin-7-O-glucuronide interacted with Trp20, Asp43, Tyr209, Cys298.

– Perlolyrine interacted with Trp20, Asp43, Tyr209, Cys298.

– N-feruloylserotonin interacted with Trp20, Trp111, Thr113, Asn160, Tyr209, Cys298, Leu300, Cys303.

– N-(p-Coumaroyl) Serotonin interacted with Trp20, Trp111, Asn160, Tyr209, Leu300, Cys303.

– Rosavin interacted with Trp20, Tyr48, Lys77, His110, Trp111, Asn160, Gln183.

These compounds have been previously studied and proven to exhibit many biological properties such as antioxidant, anti-diabetic, anticancer… Rosavin has demonstrated strong antioxidant properties, and it also has anti-tumor activity by promoting apoptosis and inhibiting cell proliferation [28]. 4′,7-dihydroxy-3′-methoxyflavan and Perlolyrine have also been shown to have antiproliferative activity against several cancer cell lines [29], [30]. Regarding anti-diabetic activity, Apigenin 7-O-glucuronide is a potential anti-diabetic agent through the suppression of protein tyrosine phosphatase 1B (PTP1B) [31]. In addition, Apigenin 7, 4'-dimethyl ether also demonstrated anti-diabetic

properties by inhibiting α-glucosidase and α-amylase [32]. Meanwhile, apolipoprotein E-deficient mice were less prone to atheromatous plaque development due to anti-atherogenic of N-feruloylserotonin and N-(p-Coumaroyl) Serotonin [33]. However, this is the first study to investigate the inhibitory activity of these compounds against AR. The results of molecular docking and interaction analysis consistently indicated that these 7 compounds are potential candidates for inhibiting AR activity and should be further studied for developing a diabetes complication treatment.

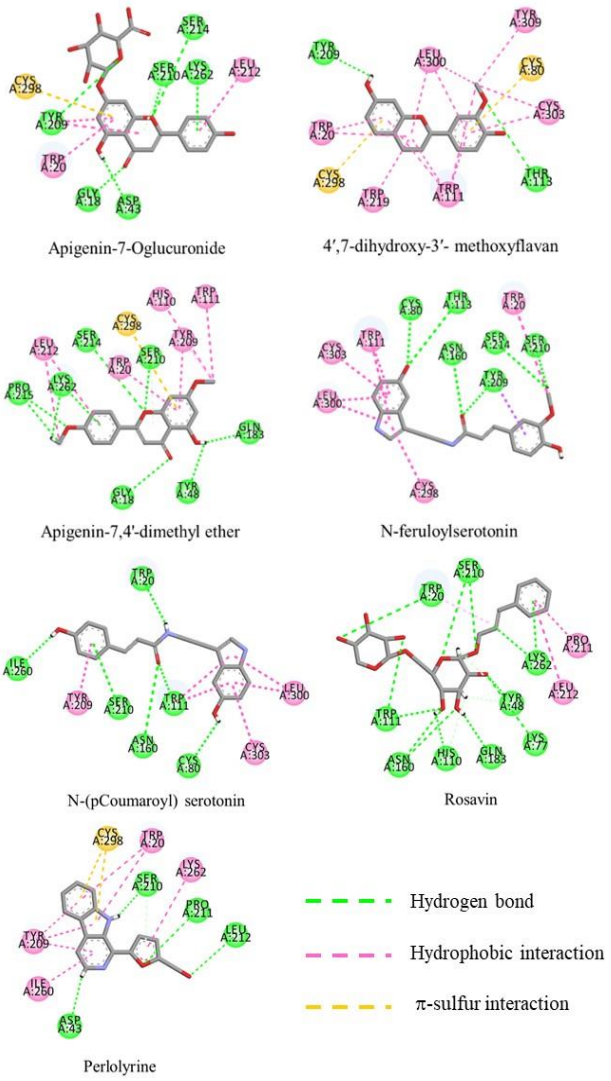
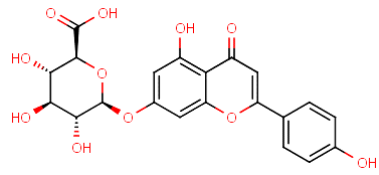
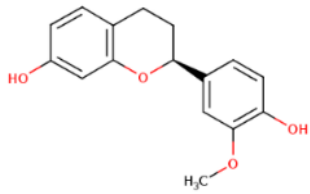
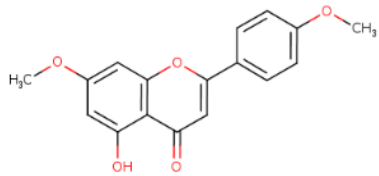
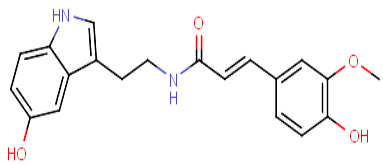
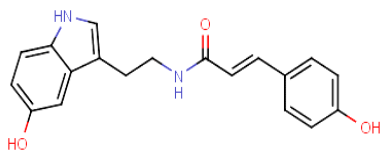
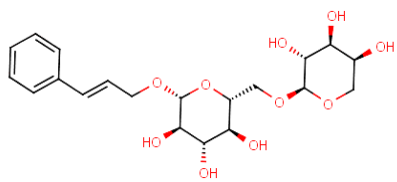
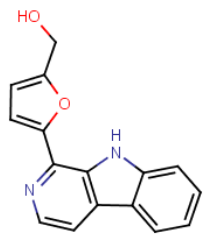


Figure 2. *Interaction between potential compound and AR*

4. Conclusion

Vietnam is a tropical country with a diverse ecosystem and a wealth of medicinal plants. Vietnamese traditional medicine has historically utilized these medicinal plant resources to cure diseases and promote wellness. In an effort to evaluate the effects of Vietnamese medicinal plants on diabetes complications, this study employed virtual screening to identify potential aldose reductase inhibitors from a library of 307 compounds derived from 30 medicinal plants. A total of 15 compounds with the ability to suppress AR have been identified, with 8 of them known to be active. The remaining seven compounds (Table 3), including Apigenin-7-O-glucuronide, Apigenin-7,4'-dimethyl ether, 4′,7-dihydroxy-3′-methoxyflavan, N-feruloylserotonin, N-(p-Coumaroyl) Serotonin, Rosavin, and Perlolyrine, should be studied *in vitro* and *in vivo* for developing the treatment of diabetic complications and inflammation.

Table 3. *Potential AR inhibitors from natural compounds*

No	Compound	Structure
1	Apigenin-7-O-glucuronide	
2	4′,7-dihydroxy-3′-methoxyflavan	
3	Apigenin-7,4'-dimethyl ether	
4	N-feruloylserotonin	
5	N-(p-Coumaroyl) Serotonin	
6	Rosavin	
7	Perlolyrine	

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