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IN SILICO SCREENING OF COMPOUNDS FROM *Nelumbo nucifera* LEAVES WITH INHIBITORY POTENTIAL AGAINST HMG-CoA REDUCTASE FOR THE TREATMENT OF DYSLIPIDEMIA

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ABSTRACT

Dyslipidemia (DLP) is a major risk factor for many serious cardiovascular diseases. The enzyme HMG-CoA reductase (HMGCR) plays a rate-limiting role in cholesterol biosynthesis, making it a key target in the treatment of DLP. This study utilized *in silico* screening methods to evaluate the HMGCR inhibitory potential of compounds extracted from lotus leaves (*Nelumbo nucifera*). Through molecular docking analysis, three compounds—Luteolin, Eriodictyol (5,7,3',5'-tetrahydroxyflavanone) and Kaempferol 7-O-glucoside—were found to have low binding energies with HMGCR, along with favorable drug-likeness properties and pharmacokinetic (ADMET) parameters according to Lipinski's criteria. These findings suggest the potential application of these compounds as natural HMGCR inhibitors, providing a promising direction for developing safer and more effective treatments for DLP compared to current synthetic statins. However, these findings warrant further *in vitro* and *in vivo* investigations to substantiate the observed potential.

Keywords: Nelumbo nucifera, HMG-CoA reductase, dyslipidemia, molecular docking, *in silico*, ADMET.

1. INTRODUCTION

Dyslipidemia is a metabolic disorder characterized by quantitative and/or qualitative abnormalities in lipid profiles, including elevated levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and/or reduced levels of high-density lipoprotein cholesterol (HDL-C). Dyslipidemia plays a crucial role in the initiation and progression of atherosclerosis and is considered a major risk factor for cardiovascular diseases (CVDs) [1]. Therefore, managing dyslipidemia is an essential strategy in both primary and secondary prevention of cardiovascular events.

3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), the rate-limiting enzyme in cholesterol biosynthesis, is a key molecular target for lipid-lowering drug development. Several HMGCR inhibitors, commonly known as statins (e.g., lovastatin, simvastatin, fluvastatin), have been developed and widely used in clinical practice. However, long-term use of statins has been associated with adverse effects, including myopathy, hepatotoxicity, nephrotoxicity, and an increased risk of type 2 diabetes mellitus [2]. Consequently, there is a pressing need to identify natural compounds with lower toxicity, better efficacy, and improved tolerability as potential alternatives to statins in the management of dyslipidemia.

Drug discovery and development is a complex, high-risk, and time-consuming process that spans target identification and validation, hit discovery, lead optimization, and preclinical and clinical evaluation. In recent years, computer-aided drug discovery (CADD) methods, particularly *in silico* approaches, have gained prominence for their ability to streamline and support various phases of the drug development pipeline. These methods can reduce the need for in vivo testing, support safer drug

design, enable drug repurposing, and assist medicinal chemists in rational drug design, development, and optimization [3]. Molecular docking, a key *in silico* technique, is used to predict the preferred orientation and binding mode of a ligand at the active site of a target protein [4]. Molecular docking simulations provide valuable insights into the binding affinity and potential inhibitory or activating effects of candidate compounds on their functional protein targets. Additionally, docking facilitates the identification of active site residues and favorable ligand conformations during enzyme–substrate interaction studies.

Among phytochemical constituents, flavonoids and alkaloids derived from the leaves of *Nelumbo nucifera* (lotus) have shown promising lipid-lowering and anti-obesity effects. Several studies have demonstrated the potential of these compounds in reducing cholesterol levels, particularly via HMGCR inhibition [5]. This study aims to conduct an *in silico* screening of 42 compounds extracted from *Nelumbo nucifera* leaves for their inhibitory activity against HMG-CoA reductase using molecular docking, alongside an evaluation of their drug-likeness and pharmacokinetic properties (ADMET).

2. MATERIALS AND METHODS

2.1. Molecular Docking Protocol

2.1.1. Ligand Preparation

The chemical structures of *Nelumbo nucifera* compounds and the reference drug atorvastatin (used as the positive control) were retrieved from the PubChem database (http://pubchem.ncbi.nlm.nih.gov/). The 3D structures of these ligands were downloaded in .sdf format and converted to .pdb format using Chimera software. Ligands were then optimized using the Conjugate Gradient method in Avogadro and converted to .pdbqt format with AutoDockTools.

2.1.2. Protein Preparation

The crystallographic structure of the catalytic domain of human HMG-CoA reductase was obtained from the Protein Data Bank (http://www.rcsb.org/) under PDB ID: 1HWK. This structure includes the catalytic domain complexed with co-crystallized atorvastatin at a resolution of 2.22 Å. For docking purposes, all water molecules and co-crystallized ligands were removed using Discovery Studio Visualizer 4.0. Hydrogen atoms were added, Kollman charges assigned, and the active site was redefined using MGL AutoDockTools 1.5.7.

The docking grid box for HMGCR was set with dimensions:
Size_x = 15, Size_y = 15, Size_z = 15
Grid spacing: 0.375 Å
Center coordinates: x = -12.222, y = -30.860, z = 20

Grid parameters were validated by re-docking the co-crystallized ligand (atorvastatin) to ensure that the root-mean-square deviation (RMSD) between the docked pose and the original position was ≤1.5 Å. The prepared protein was saved in .pdbqt format for docking.

2.2. Molecular Docking Simulation

After validation, molecular docking of the 42 phytocompounds and the reference drug (atorvastatin) into the active site of HMGCR was performed using AutoDock Vina.

2.3. Lipinski's Rule of Five Evaluation

The drug-likeness of the compounds was assessed using the Lipinski's Rule of Five via the online tool (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp). Input data included molecular weight, number of hydrogen bond donors and acceptors, LogP, and molar refractivity. Compounds were downloaded from PubChem, and a physiological pH of 7 was used as input. Compounds were considered to have favorable drug-likeness if they satisfied at least 3 out of the following 5 criteria:

(1) Molecular weight < 500 Da
(2) LogP < 5
(3) ≤5 hydrogen bond donors
(4) ≤10 hydrogen bond acceptors
(5) Molar refractivity between 40–130

2.4. Pharmacokinetics and Toxicity Prediction

Compounds that satisfied drug-likeness criteria were subjected to ADMET prediction using the pkCSM web server, with SMILES strings retrieved from PubChem. The evaluated parameters included absorption (water solubility, Caco-2 permeability, and intestinal absorption), distribution (volume of distribution at steady state [VDss], blood–brain barrier [BBB] permeability, and central nervous system [CNS] permeability), metabolism (substrate potential for cytochrome P450 isoforms, including CYP2D6 and CYP3A4), excretion (renal clearance), and toxicity (AMES mutagenicity, hepatotoxicity, hERG inhibition, and skin and liver toxicity). Based on these pharmacokinetic and toxicological profiles, the most promising candidate compound was identified for further investigation.

3. RESULTS

3.1. Validation of the Docking Model

Prior to the virtual screening of candidate compounds, re-docking of the co-crystallized ligand into the active site of the target protein was performed to validate the accuracy of the docking protocol. The structural similarity between the original and re-docked ligand conformations was evaluated using the root-mean-square deviation (RMSD) value, calculated with Chimera software. The results demonstrated a high degree of conformational overlap between the ligand structures before and after docking, with an RMSD value of 1.011 Å (< 1.5 Å). This indicates that the docking procedure was accurately established and is suitable for reliable virtual screening of other compounds.

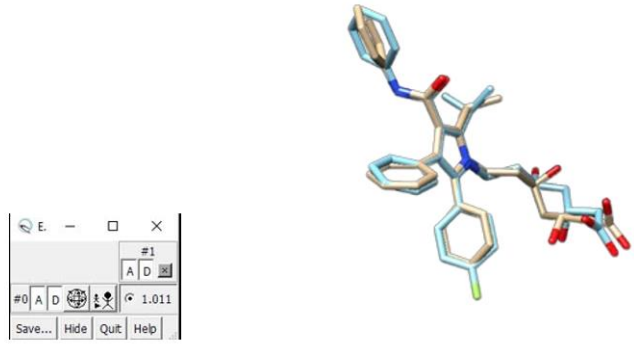

Figure 1. RMSD of co-crystallized atorvastatin before and after re-docking

3.2. Molecular docking analysis

All 42 phytochemicals extracted from *Nelumbo nucifera* leaves, along with the reference compound atorvastatin, were subjected to molecular docking with HMG-CoA reductase (HMGCR) to identify potential inhibitors of the enzyme. The docking result of the positive control was used as a benchmark for selecting promising candidate compounds during the screening process. For the co-crystallized ligand of HMGCR, docking results showed that atorvastatin exhibited a binding energy (ΔG) of −8.0 kcal/mol. Hydrogen bonds were formed between the HMG-CoA-like moiety of atorvastatin and several key amino acid residues of HMGCR, including Ser684, Lys692, Asn755, Lys735, and Arg590. Additionally, the fluorophenyl substituent formed hydrogen bonds with Arg590 and Ser661.

The hydrophobic ring structure of atorvastatin also engaged in multiple interactions:
– Hydrogen bonds with Ser684, Lys692, Arg590, Lys735, Ser661, Ser565, and Asn755
– π-alkyl interaction with Leu853
– π–sigma interaction with Ala856
– A hydrogen bond between the carbonyl oxygen of atorvastatin and Ser565 of HMGCR

Furthermore, van der Waals interactions were observed between the ligand and various amino acid residues within the active site of the enzyme. The molecular interactions between atorvastatin and HMGCR are illustrated in Figure 2**.**

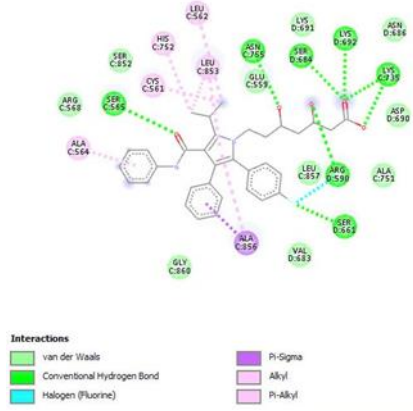

Figure 2. Two-dimensional illustration of binding interactions between the reference compound atorvastatin and the active site of HMG-CoA reductase.

The docking results revealed that the reference compound formed interactions with several key amino acid residues within the active site of HMGCR. As a type II statin, atorvastatin demonstrated a favorable docking score and formed multiple interactions with catalytically important residues. Its binding energy (ΔG) of −8.0 kcal/mol served as a reference threshold for selecting potential lead compounds.

By comparing the binding affinities of the 42 *Nelumbo nucifera* compounds to that of atorvastatin, candidates exhibiting lower or comparable binding energies (ΔG ≤ −8.0 kcal/mol) were shortlisted as potential HMGCR inhibitors.

Table 1. Docking results of compounds with the HMG-CoA reductase (HMGCR) target

No.	Compound	Binding Energy (kcal/mol)	No.	Compound	Binding Energy (kcal/mol)
1	Anonaine	-7.6	23	()-boscialin	-6.0
2	Armefapavine	-6.8	24	Hyperoside	-8.6
3	Coclaurine	-7.6	25	elephantorrhizol	-8.5
4	Dehydroanonaine	-8.0	26	Leucocyanidin	-7.7
5	Dehydroemetine	-6.7	27	Leucodelphinidin	-8.0
6	Dehydronuciferin	-7.4	28	Quercetin 3-O-glucuronide	-8.4
7	(6R,6aR)-Roemerine-Nb-oxide	-8.3	29	Quercetin 3-O-β-D-galactopyranoside	-8.4
8	Lirinidine	-8.5	30	Rutin	-10.1
9	Liriodenine	-9.0	31	(+)-Dehydrovomifolio	-6.0
10	Lotusine	-7.2	32	Vomifoliol	-6.2
11	Nelumboside	-8.7	33	oleracein E	-7.6
12	N-Methylcoclaurine	-7.3	34	Norcoclaurine (higenamine)	-7.7
13	N-nornuciferine	-6.9	35	Annuionone D	-5.8
14	Nuciferine	-7.0	36	Quercetin	-8.0
15	Pronuciferine	-7.0	37	Isoquercitrin	-8.2
16	Trans-N-coumaroyltyramine	-7.1	38	(+)-Epiloliolide (Isololiolide)	-5.9
17	Cis-N-coumaroyltyramine	7.4	39	trans-N-feruloyltyramine	-8.0

18	(+)-Catechin	-8.1	40	cis-N-feruloyltyramine	-6.8
19	Astragalin	-7.8	41	Kaempferol 7-O-glucoside	-8.0
20	luteolin	-8.5	42	Eriodictyol	-8.0
21	taxifolin	-8.2	43	Atorvastatin positive control	-8.3
22	epitaxifolin	-7.8			

3.3. Lipinski's Rule of Five

Table 2. Screening Results of Drug-like Compounds Based on Lipinski's Rule of Five

No.	Compound		Molecular Weight	Number of Hydrogen Bond Donors	Number of Hydrogen Bond Acceptors	LogP	Molar Refractivity (MR)
1	(6R,6aR)-Roemerine-Nb-oxide		279.000000	0	3	3.167399	80.779976
2	Lirinidine		281.000000	1	3	3.152899	82.873772
3	Liriodenine		275.000000	0	4	2.234540	76.325989
4	Nelumboside		640.000000	11	18	-2.814101	139.457291
5	Hyperoside		464.000000	8	12	-0.730600	106.273842
6	elephantorrhizol		322.000000	7	8	0.957299	75.952568
7	Quercetin 3-O-glucuronide		478.000000	8	13	-0.638300	106.823845
8	Quercetin 3-O-β-D-xylopyranosyl-β-D-galactopyranoside		464.000000	8	12	-0.730600	106.273842
9	Rutin		610.000000	10	16	-1.878800	137.495483
10	Dehydroanonaine		263.000000	1	3	3.689698	79.770683
11	(+)-Catechin		290.000000	5	6	1.546100	72.622978
12	taxifolin		304.000000	5	7	1.186300	73.249474
13	luteolin		286.000000	4	6	2.125199	72.478676
14	Leucodelphinidin		322.000000	7	8	0.742600	75.543564
15	Quercetin		302.000000	5	7	2.010900	74.050476
16	Isoquercitrin		464.000000	8	12	-0.730600	106.273842
17	trans-N-feruloyltyramine		313.000000	3	7	2.478499	88.513275
18	Kaempferol 7-O-glucoside		448.000000	4	8	-0.221600	105.116051
19	Eriodictyol		288.000000	4	6	2.215499	71.859680

The results showed that 19 out of 42 compounds satisfied at least 2 out of the 5 criteria defined in Lipinski's Rule of Five. Notably, 8 compounds-(6R,6aR)-Roemerine-Nb-oxide, Lirinidine, Liriodenine, Dehydroanonaine, Luteolin, trans-N-feruloyltyramine, Kaempferol 7-O-glucoside, and Eriodictyol-met all five criteria, indicating a high potential for drug-likeness.

Although some compounds, such as Rutin (−10.1 kcal/mol), exhibited significantly lower binding energies compared to the reference compound, they did not fulfill Lipinski's criteria and are therefore less promising in terms of drug development potential.

3.4. ADMET Prediction

The absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles of compounds meeting Lipinski's criteria were predicted using the pkCSM tool. Table 3 below presents the predicted ADMET properties of the 8 compounds that satisfied all five Lipinski's rules.

Table 3. Predicted ADMET profiles of selected compounds: absorption; distribution and metabolism; excretion and toxicity

Parameters	(6R,6aR)-Roemerine-Nb-oxide	Lirinidine	Liriodenine	Dehydroanonaine	luteolin	trans-N-feruloylytyramine	kaempferol 7-O-glucoside	Eriodictyol
Absorption								
Water Solubility (log mol/L)	-3.814	-4.054	-3.586	-4.229	-3.094	-3.292	-2.746	-3.177
Caco-2 Permeability (log Papp in 10^{-6} cm/s)	1.716	1.632	1.258	1.672	0.096	0.925	0.353	-0.089
Human Intestinal Absorption (%)	96.771	95.415	100	94.157	81.13	90.23	30.716	72.672
Distribution								
VDss (log L/kg)	1.3	1.233	-0.199	0.476	1.153	0.128	1.018	0.196
Blood–Brain Barrier (BBB) Permeability (log BBB)	0.321	0.476	-0.03	0.274	-0.907	-0.715	-0.465	-0.815
Metabolism								
CYP2D6 Substrate	Yes	Yes	No	Yes	No	No	No	No
CYP3A4 Substrate	Yes	Yes	Yes	Yes	No	Yes	No	No
CYP2D6 Inhibitor	Yes	Yes	No	Yes	No	No	No	No
CYP3A4 Inhibitor	No	No	No	No	No	Yes	No	No
Excretion								
Total Clearance (log mL/min/kg)	1.023	0.997	0.179	0.179	0.495	0.27	0.457	0.404
Renal OCT2 Substrate	No	No	No	No	No	No	No	No
Toxicity								
AMES Toxicity	Yes	No	No	Yes	No	No	No	No
hERG Inhibitor	No	No	Yes	No	No	No	No	No
Acute Oral Toxicity in Rats (LD_{50})	2.882	2.587	2.926	2.663	2.455	1.873	2.552	2.059
Hepatotoxicity	Yes	Yes	Yes	No	No	Yes	No	No
Skin Sensitization	No	No	No	No	No	No	No	No

Based on the results of molecular docking and ADMET analysis, the compounds luteolin, kaempferol 7-O-glucoside, and eriodictyol were selected as the top candidates with the most favorable pharmacokinetic and toxicity profiles. The 2D and 3D interactions of these three molecules with HMG-CoA reductase (HMGCR) were visualized and illustrated using Discovery Studio Visualizer 4.0, as shown in Figures 3, 4, and 5, respectively.

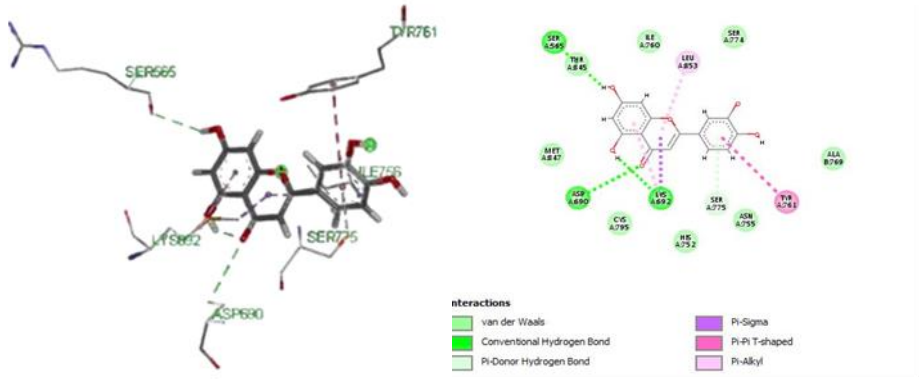

Figure 3. Interaction of Luteolin with HMG-CoA Reductase (HMGCR)

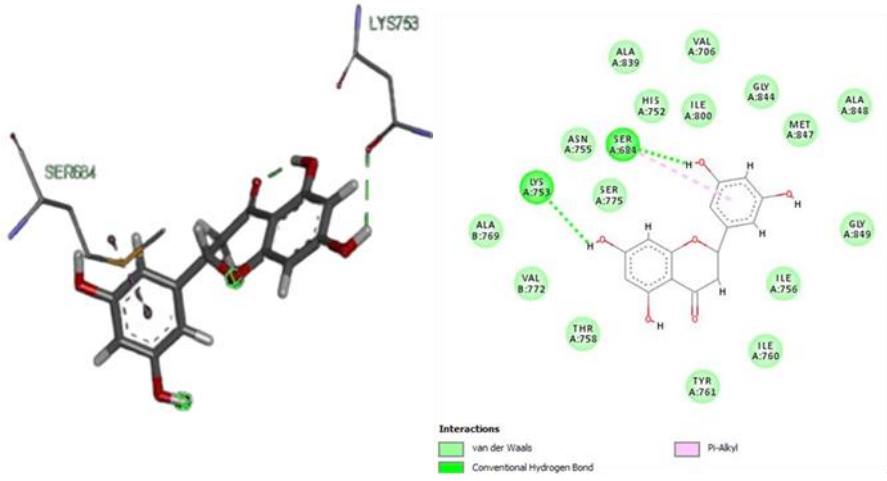

Figure 4. Interaction of Eriodictyol with HMG-CoA Reductase (HMGCR)

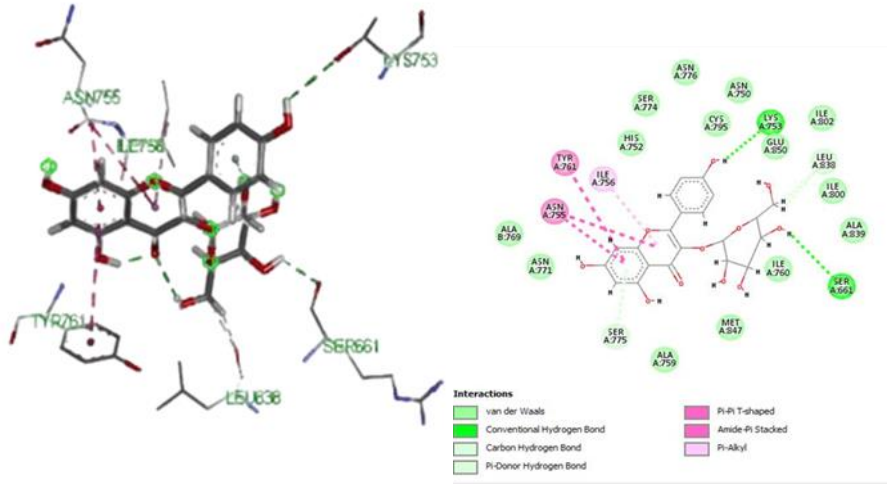

Figure 5. Interaction of Kaempferol 7-O-glucoside with HMG-CoA Reductase (HMGCR)

In terms of binding interactions, all three compounds exhibited strong affinity at the active site of HMG-CoA reductase (HMGCR) by interacting with key amino acid residues. A comparison of their

molecular interactions revealed that all compounds formed multiple hydrogen bonds, primarily involving hydroxyl (–OH) and carbonyl (C=O) groups with amino acid residues of HMGCR.

Table 4. Molecular interactions of potential compounds with HMGCR

Compound	Binding energy (kcal/mol)	Interacting amino acid residues
Luteolin	-8.5	Ser565,Asp690,Lys692, Tyr761, Leu853, Ser775
Eriodictyol	-8.0	Ser648, Lys753
Kaempferol 7-O-glucoside	-8.0	Lys 753, Ser661, Ser775 Leu838
Atorvastatin positive control	-8.0	Ser684, Lys692, Asn755, Lys735, Arg590, Ser661, Ser565, Leu853, Ala856

4. DISCUSSION

From 42 compounds extracted from lotus leaves (*Nelumbo nucifera*) and retrieved from the PubChem database, molecular docking with the HMG-CoA reductase (HMGCR) enzyme identified 19 compounds with high binding affinities. Eight compounds met all criteria of Lipinski's Rule of Five, indicating good drug-likeness. Based on pharmacokinetic and toxicity screening, three outstanding candidates were selected: luteolin (ID: 5280445), eriodictyol (ID: 440735), and kaempferol 7-O-glucoside (ID: 10095180).

4.1. Luteolin

Luteolin, also known as 3',4',5,7-Tetrahydroxyflavone, with the molecular formula $C_{15}H_{10}O_6$, is a naturally occurring flavonoid present in various medicinal plants. It has demonstrated beneficial effects including anti-tumor, antioxidant, and anti-inflammatory activities [6]. Previous studies have shown that luteolin isolated from *Matricaria recutita L.* (Chamomile) exerts cholesterol-lowering effects in animal models [7]. Another study revealed that luteolin can suppress the translocation of SREBP-2—a key regulator of HMGCR expression—via an AMPK-dependent pathway. Immunohistochemistry images confirmed that luteolin significantly reduced intracellular SREBP-2 levels [8]. In this study, luteolin exhibited strong binding affinity to HMGCR with a docking score of –8.5 kcal/mol. It also demonstrated good oral absorption (81.13%) and moderate Caco-2 membrane permeability (0.096 log Papp in 10^{-6} cm/s). Importantly, no hepatotoxicity, cardiotoxicity, or skin sensitization was observed. However, further in-depth studies are necessary to assess its broader toxicity profile and validate its HMGCR inhibitory activity experimentally.

4.2. Eriodictyol

Eriodictyol (5,7,3',5'-tetrahydroxyflavanone) is a flavanone-type flavonoid commonly found in citrus fruits, vegetables, and medicinal plants, especially *Eupatorium arnottianum* and *Yerba Santa*, a native North American herb. Eriodictyol is recognized as a potent natural agent with therapeutic benefits including neuroprotection, cardioprotection, hepatoprotection, anti-diabetic, anti-obesity, skin protection, analgesic, antioxidant, anti-inflammatory, antipyretic, and anti-tumor activities [9]. A study combining green tea extract with eriodictyol improved hypercholesterolemia and downregulated hepatic cholesterol synthesis enzymes such as HMGCR and HMGCS, while upregulating LDLR expression in mice fed a high-fat, high-sugar diet [10]. It also increased total antioxidant capacity, reduced IL-6, MCP-1, and hs-CRP levels, and mitigated hepatic lipid accumulation and damage, suggesting potential in preventing cardiovascular disease-associated metabolic changes [11]. In this study, eriodictyol showed a docking score of –8.0 kcal/mol with HMGCR, relatively good human intestinal absorption (72.67%), but poor Caco-2 permeability (–0.089 log Papp in 10^{-6} cm/s), indicating limited membrane transport. While it showed no hepatotoxicity, cardiotoxicity, or skin sensitization, its oral bioavailability may need enhancement for drug development.

4.3. Kaempferol 7-O-glucoside

Kaempferol 7-O-glucoside is a flavonoid found in several plants such as *Menosa chinensis Benth* and *Diospyros kaki L.* (persimmon), known for antioxidant and lipid-lowering effects [12]. Matsumoto et al. (2006) demonstrated that fruits and leaves of *Diospyros kaki* significantly reduced plasma cholesterol and triglyceride levels in rats, confirming its anti-atherosclerotic properties [13]. The compound is also found in the leaves of *Lycium chinense* (Lycii folium, LF), which are widely consumed as food and functional tea in China and Southeast Asia, and has been reported to exhibit anti-obesity, antioxidant, and lipid-lowering effects in obese animal models. In the present study, kaempferol 7-O-glucoside demonstrated a docking score of −8.0 kcal/mol against HMGCR; however, it showed low predicted human intestinal absorption (30.71%) and moderate Caco-2 permeability (0.353 log Papp $\times 10^{-6}$ cm/s), indicating limited oral bioavailability and membrane permeability. Despite its non-toxic profile (no hepatotoxicity, cardiotoxicity, or skin sensitization), it scored the lowest among the three candidates, highlighting the need for further studies to verify its inhibitory effect on HMGCR and assess its drug development potential.

5. CONCLUSION

This study conducted virtual screening of 42 compounds derived from *Nelumbo nucifera* (lotus leaf) to identify potential inhibitors of HMG-CoA reductase for the development of anti-hyperlipidemic drugs. The results identified three promising candidates-luteolin, eriodictyol, and kaempferol 7-O-glucoside-that exhibit both inhibitory activity toward HMGCR and favorable pharmacokinetic properties. Further in vitro and in vivo experimental studies are warranted to confirm the therapeutic potential of these compounds.

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