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Original Article

Elucidating the Lipid-lowering Mechanism of 6-Gingerol: A Molecular Docking Study Targeting HMG-CoA Reductase, PPAR-α, and CETP

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Abstract: Hyperlipidemia is a major risk factor for atherosclerosis and contributes to the growing global burden of cardiovascular diseases, myocardial infarction, and metabolic syndrome. 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), Peroxisome proliferator-activated receptor alpha (PPAR-α), and Cholesteryl Ester Transfer Protein (CETP) are the important determinants of hyperlipidemia by regulating a plethora of transcriptional factors in metabolically active tissues such as adipose tissue, liver, and skeletal muscle. The present study aimed to evaluate the binding affinity of 6-Gingerol ((S)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone) with therapeutic target proteins of hyperlipidemia using an *in silico* approach. The *in silico* docking studies were performed between 6-Gingerol (PubChem CID: 442793) and HMG-CoA reductase, PPAR-α, and CETP with PDB IDs of 1HW9, 6KXX, and 2OBD, respectively, by using AutoDock Tools 1.5.6. Our results revealed that 6-Gingerol exhibited maximum binding affinities with PPAR-α (-7.2), followed by HMG-CoA reductase (-6.2) and CETP (-6.1) kcal/mol. The docking validation showed RMSD values below 1.5 Å, confirming the reliability and reproducibility of the docking protocol. Furthermore, 6-gingerol satisfied all of Lipinski's rule of five criteria, exhibited favorable ADMET characteristics, and showed negligible toxicity *in silico*. Therefore, the 6-gingerol compound shows potential as a multi-target lipid-lowering candidate.

Keywords: 6-Gingerol, HMG-CoA reductase, Peroxisome proliferator-activated receptor alpha (PPAR-α), Cholesteryl Ester Transfer Protein, Lipid-Lowering Mechanism.

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1. Introduction

Hyperlipidemia is a disorder of human lipid metabolism or transport, primarily characterized by abnormally elevated levels of total cholesterol (TC), triglycerides (TGs), and low-density lipoprotein cholesterol (LDL-C) in the blood [1]. It is a risk factor for atherosclerotic cardiovascular diseases (ASCVD), obesity, and diabetes. Statistics show an upward trend of dyslipidemia among the adult population in Vietnam. The overall prevalence of having at least one component of dyslipidemia was 49% (95%CI = 38%-60 %), and figures for high total cholesterol, elevated triglycerides, increased low-density lipoprotein-cholesterol and low high-density lipoprotein-cholesterol were 31% (95%CI = 25 %; 37 %), 38 % (95%CI = 31%; 44%), 21% (95%CI = 12%; 32%), 23% (95%CI = 16%; 30%), respectively [2]. Despite the availability of various synthetic lipid-lowering agents such as statins and fibrates, long-term use of statins has been associated with muscle-related adverse events, including myopathy and myalgia [3] while fibrates are associated with a slightly increased risk (<1.0%) for myopathy, cholelithiasis, and venous thrombosis [4]. Thus, the discovery of safer natural compounds with lipid-lowering potential has gained significant attention.

6-Gingerol, the major bioactive component of *Zingiber officinale* (ginger), has been reported to exhibit antioxidant, anti-inflammatory, and cardioprotective activities. Ginger has a beneficial role in metabolic syndrome treatment due to its hypotensive, anti-obesity, hypoglycemic, and hypolipidemic effects. It can significantly reduce atherosclerotic lesion areas, VLDL, and LDL cholesterol levels [5]. However, its precise molecular mechanism in regulating lipid metabolism remains unclear. In this study, molecular docking was employed to elucidate the potential inhibitory interactions of 6-gingerol with three key proteins involved in lipid regulation-HMG-CoA reductase**,** PPAR-α, and CETP-to provide molecular insights into its hypolipidemic mechanism.

3-Hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) is a rate-limiting enzyme that catalyzes the conversion of HMG-CoA to mevalonate, a key step in the cholesterol biosynthetic pathway. An increase in HMG-CoA reductase activity leads to enhanced endogenous cholesterol synthesis, whereas regulation or inhibition of this enzyme results in a reduction of cholesterol production. Competitive inhibitors of HMG-CoA reductase (typically the statin class) decrease hepatic cholesterol synthesis, upregulate LDL receptors on hepatocyte membranes, and thereby enhance the hepatic uptake of LDL-C [6]. Consequently, inhibition of HMG-CoA reductase represents a well-established therapeutic strategy for lowering plasma cholesterol.

Among the nuclear receptors involved in lipid regulation, PPAR-α plays a particularly crucial role in hepatic lipid oxidation. Peroxisome proliferator-activated receptor alpha (PPAR-α) is a member of the nuclear hormone receptor superfamily that plays a central role in lipid metabolism. It regulates a network of genes involved in fatty acid uptake, esterification, transport, and lipoprotein metabolism [7]. Upon activation, PPAR-α forms a heterodimer with the retinoid X receptor (RXR) and binds to specific PPAR response elements (PPREs) in the promoter regions of target genes, thereby enhancing lipolysis and fatty acid β-oxidation [8]. Clinically, pharmacological activation of PPAR-α by fibrates effectively ameliorates dyslipidemia by significantly reducing plasma triglycerides, modestly elevating plasma HDL-C, and slightly decreasing plasma LDL-C levels [8]. In addition to synthetic ligands such as fibrates, PPAR-α can also be activated by endogenous fatty acids and natural compounds, suggesting that dietary bioactive molecules like 6-gingerol may exert hypolipidemic effects through PPAR-α modulation.

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein synthesized primarily in the liver and adipose tissue and secreted into the circulation [9], where it mediates the exchange of cholesteryl esters from high-density

lipoproteins (HDL) to apolipoprotein B (apoB)-containing lipoproteins such as very-low-density lipoproteins (VLDL) and low-density lipoproteins (LDL), in exchange for triglycerides [10]. This process facilitates the indirect pathway of reverse cholesterol transport, in which apoB-containing lipoproteins subsequently deliver cholesterol to the liver via hepatic LDL receptors. Structural imaging studies have shown that CETP forms a hydrophobic tunnel between HDL and LDL particles, allowing direct lipid transfer [11].

Epidemiological evidence demonstrates an inverse relationship between plasma HDL-C levels and the risk of coronary artery disease, and experimental data have confirmed the atheroprotective function of HDL. These findings have made HDL modulation—particularly CETP inhibition—an attractive therapeutic approach to complement statin therapy in reducing cardiovascular risk [9]. Inhibition of CETP activity increases cholesteryl ester retention within HDL, resulting in elevated HDL-C levels and reduced LDL-C levels, thereby enhancing reverse cholesterol transport and promoting cardioprotection. However, several CETP inhibitors, including torcetrapib and dalcetrapib, have failed in phase III clinical trials due to drug-induced adverse effects such as elevated blood pressure, hyperaldosteronism [12], and increased response to endothelin in the vasculature [13], underscoring the urgent need to identify safer and more effective natural CETP inhibitors such as 6-gingerol.

Molecular docking is an effective *in silico* approach to predict ligand–protein binding modes and affinities, thereby elucidating potential molecular mechanisms. It determines the optimal configuration, spatial orientation, and stability of complexes at their lowest energy levels [14]. We employed AutoDock Vina with re-docking validation and complemented docking with Lipinski, SwissADME, and pkCSM analyses to assess drug-likeness and ADMET properties of 6-gingerol. This study aimed to evaluate the binding interactions of 6-gingerol with HMG-CoA reductase, PPAR-α, and CETP via molecular docking, and to predict pharmacokinetic and toxicity profiles to assess its potential as a lipid-lowering agent.

2. Materials and Methods

2.1. Molecular Docking

Preparation of protein structures:

The 3D structures of the target proteins were retrieved from the Protein Data Bank (PDB) (https://www.rcsb.org): HMG-CoA reductase (PDB ID: 1HW9), Peroxisome proliferator-activated receptor alpha (PDB ID: 6KXX), and Cholesteryl ester transfer protein (PDB ID: 2OBD). Each structure contained its respective crystallised ligand: SIM (Simvastatin acid), T02 (1-(4-chlorophenyl)-6-methyl-3-propan-2-yl-pyrazolo[3,4-b]pyridine-4-carboxylic acid), and EPE (4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid).

The active sites of the target proteins were determined using Discovery Studio Visualizer 4.0. Water molecules and co-crystallized ligands were removed, and then hydrogen atoms were added using AutoDock Tools 1.5.6. The positions of the active sites were then redefined with Molecular Graphics Laboratory (MGL) AutoDock Tools 1.5.6, as summarized in Table 1. The coordinates of the grid box (XYZ) were defined based on the position of the co-crystallized ligand (native ligand) in each protein structure obtained from the PDB, ensuring that the docking simulations were performed at the experimentally validated active sites.

Table 1. The active sites of three important protein targets

PDB ID	Grid box size (Å)	Grid spacing (Å)	(XYZ)
1HW9	40x40x40	0.375	(7.835, -14.846, 12.623)
6KXX	40x40x40	0.375	(5.736, -11.482, -24.201)
2OBD	40x40x40	0.375	(14.572, 4.077, 39.553)

Preparation of ligand structures:

The 3D structure of 6-gingerol, with the International Union of Pure and Applied Chemistry (IUPAC) name ((S)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone), was retrieved from the PubChem database (https://pubchem. ncbi.nlm.nih.gov) in SDF format and converted to PDB format using UCSF Chimera 1.18 software. The molecule was first optimized through the Conjugate Gradients method in Avogadro software and then converted to PDBQT format using AutoDock Tools 1.5.6.

Docking procedure:

6-Gingerol was docked into the active site of the protein using AutoDock Vina (via AutoDock Tools 1.5.6) software. Docking parameters were set to an exhaustiveness of 8, with the number of output binding modes (num_modes) set to 9 for each protein–ligand complex to ensure adequate conformational sampling. Discovery Studio Visualizer 4.0 software was utilised to observe the interactions between the proteins and 6-gingerol.

Docking results evaluation:

Using Discovery Studio 2019 Client, the co-crystallised ligand was separated from the protein, saved in PDB format, and then converted to PDBQT format by AutoDock Tools 1.5.6. The co-crystallised ligand was re-docked into the active site of the target protein. The docking process is considered successful and reliable if the root mean square deviation (RMSD) value does not exceed 1.5 Å. For 6-gingerol, the binding affinity was evaluated based on its interactions with amino acid residues at the active site, and the binding energy was calculated using the scoring function of AutoDock Vina.

2.2. Evaluation of Lipinski's Rule of Five Criteria

We used Lipinski's rule of five online tool (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) to assess the potential of 6-gingerol as a therapeutic drug. The chemical structure of 6-gingerol was downloaded from the PubChem database in SDF format and set at pH 7.0. A compound is considered "drug-like" if it meets at least 2 of the 5 criteria: molecular weight (MW), high lipophilicity (LogP), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), and molar refractivity (MR) [15]. After the drug-like compound was selected, further analyses of pharmacokinetic properties, toxicity, and molecular dynamics were carried out to obtain the final results.

2.3. Prediction of Pharmacokinetic and Toxicity Parameters

The pkCSM online tool (http://biosig.unimelb.edu.au/pkcsm/prediction, accessed on 20 August 2025) was employed by inputting the compound's SMILES formula to predict the pharmacokinetic parameters, including absorption, distribution, metabolism, excretion, and toxicity (ADMET) of 6-gingerol. These predictions are crucial for assessing the compound's potential success as a drug candidate.

2.4. Bioavailability Radar

A bioavailability radar was utilized to assess the drug-likeness of 6-gingerol. The analysis was conducted using the SwissADME online platform (http://www.swissadme.ch/index.php, accessed on 20 August 2025) [16], which generates a radar plot based on six key physicochemical parameters: lipophilicity, size, polarity, solubility, flexibility, and saturation. In this model, the compounds whose radar plots fall within the pink area are considered to exhibit favorable drug-like characteristics.

3. Results

3.1. Validation of Molecular Docking

Before compound screening, the accuracy of the molecular docking model must be validated. The re-docking process produced RMSD values of 0.971 Å, 0.088 Å, and 1.083 Å, respectively (Figure 1). Since all values are below the 1.5 Å threshold, the docking protocol can be considered accurate and reliable for subsequent analyses of the target proteins.

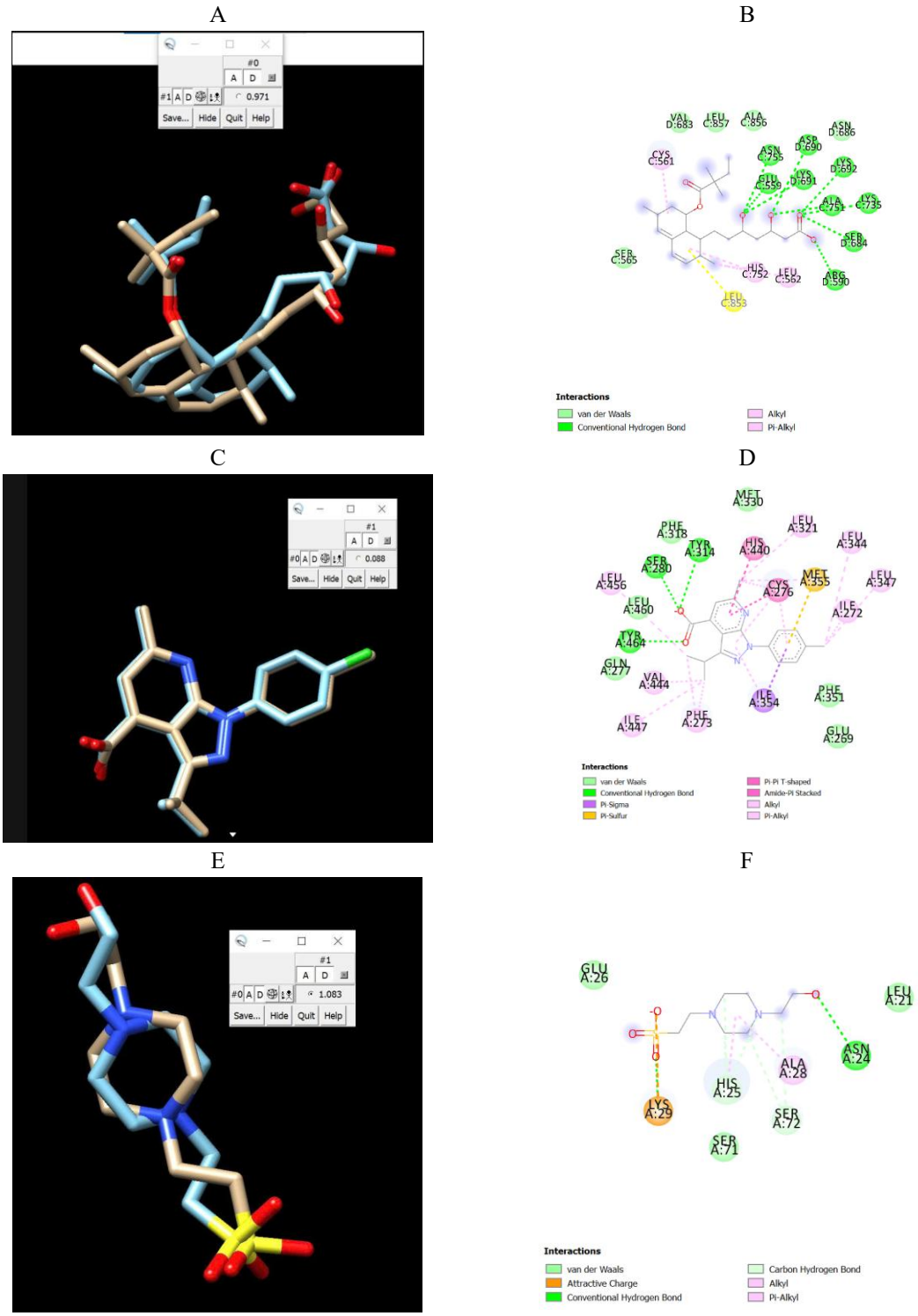

Figure 1. (A) Re-docking validation results of SIM and 1HW9, (B) 2D interaction between SIM and 1HW9, (C) Re-docking validation results of T02 and 6KXX, (D) 2D interaction between T02 and 6KXX, (E) Re-docking validation results of EPE and 2OBD, (F) 2D interaction between EPE and 2OBD.

3.2. Docking Results of 6-Gingerol on Protein Targets

After ligand preparation, molecular docking was performed to evaluate the potential inhibitory effect of 6-gingerol against hyperlipidemia-related targets. The compound demonstrated binding energies of -6.2, -7.2, and -6.1 kcal/mol toward HMG-CoA reductase, peroxisome proliferator-activated receptor alpha (PPAR-α), and cholesteryl ester transfer protein (CETP), respectively. For comparison, the co-crystallized ligands-SIM, T02, and EPE-showed binding affinities of -6.7, -10.3, and -5.2 kcal/mol, with the same targets.

Binding energy (kcal/mol) correlates with the binding affinity of ligands or inhibitors to their respective target proteins. Generally, lower binding energy signifies higher affinity between ligand and receptor. These results indicate that 6-gingerol exhibits moderate binding affinities toward these targets—HMG-CoA reductase, PPAR-α, and CETP—and shows weaker binding affinity compared to the corresponding co-crystallized ligands for HMG-CoA reductase and PPAR-α, but stronger binding than the native ligand of CETP.

3.3. Results of Lipinski's Rule of Five

A compound is considered "drug-like" when it meets at least two out of the five parameters defined by Lipinski's rule of five: i) Molecular weight < 500 Dalton; ii) High lipophilicity (logP<5); iii) Less than 5 hydrogen bond donors; iv) Less than 10 hydrogen bond acceptors; v) Molar refractivity between 40-130 [15]. The compliance of 6-gingerol with these criteria is summarised in Table 2 below. The results indicate that 6-gingerol satisfies all five criteria, suggesting it possesses highly drug-like properties.

Table 2. Results of Lipinski's rule of five

Compound	Molecular weight < 500 Dalton	High lipophilicity (logP<5)	Less than 5 hydrogen bond donors	Less than 10 hydrogen bond acceptors	Molar refractivity between 40-130
6-Gingerol	294	3.233	2	4	82.752

3.4. Absorption, Distribution, Metabolism, Excretion, and Toxicity Prediction

The predicted results for ADMET, including absorption, distribution, metabolism, excretion, and toxicity, are presented in Table 3.

The absorption potential of the compounds was evaluated based on three main parameters: water solubility, permeability through Caco2 membranes, and intestinal drug absorption rate. A compound is considered to have good absorption when the $\log_{10}$ of its molar water solubility exceeds -4, and its Caco2 permeability value is above 0.9 [17]. The results presented in Table 3 indicate that 6-gingerol exhibits a Caco2 permeability value exceeding 0.9 (0.94), suggesting a high membrane permeability potential. Furthermore, 6-gingerol demonstrates good water solubility (-3.164) and an excellent intestinal absorption rate of approximately 92%.

In terms of distribution, compounds are considered to be well-distributed into tissues when their log VDss values exceed 0.45, and poorly distributed when below -0.15 [17]. A higher VDss value indicates a greater extent of drug distribution into tissues relative to plasma. 6-Gingerol exhibited a log VDss of 0.524, indicating good tissue distribution.

The inability to cross the blood–brain barrier (BBB) is clinically significant for reducing toxicity, minimizing adverse effects, and enhancing the efficacy of drugs that are not intended to target the central nervous system. Compounds are generally capable of penetrating the BBB if their logBB values exceed 0.3.

However, 6-gingerol was predicted not to cross the BBB, as indicated by its logBB value of -0.727.

From the aspect of metabolism, CYP2D6 and CYP3A4 are the two major polymorphic isoforms of the cytochrome P450 enzyme family involved in hepatic drug metabolism. Inhibitors of P450 enzymes can significantly alter drug pharmacokinetics. 6-Gingerol was found to be neither a substrate nor an inhibitor of CYP2D6 or CYP3A4, suggesting that it does not interfere with these metabolic pathways.

In terms of excretion, the pharmacokinetic property of 6-gingerol was evaluated based on its total clearance. The compound is excreted via the kidneys with a total clearance value of 1.339.

Regarding toxicity, 6-gingerol is predicted to be non-toxic based on the AMES test, non-hepatotoxic, and non-sensitising to the skin.

Based on the predicted ADMET results, 6-gingerol exhibits the following pharmacokinetic characteristics: good absorption (as evidenced by high Caco2 permeability, good water solubility, and excellent intestinal absorption), adequate tissue distribution (VDss = 0.524 > 0.45), unable to cross the BBB, and no substrate or inhibitory activity toward main hepatic enzymes (CYP2D6 and CYP3A4), indicating no adverse impact on hepatic efficacy or toxicity. It is excreted through the kidneys with a total clearance of 1.339 (log mL/min/kg) and shows no hepatotoxicity, dermatotoxicity, or AMES toxicity.

However, further in-depth investigations are required to optimize and address the limitations of this compound, thereby positioning 6-gingerol as a promising natural candidate for the development of lipid-lowering therapy.

Table 3. Predicted pharmacokinetic and toxicity results

Properties	Criterias	Results
Absorption		
Water solubility (log mol/L)	>-4 good; -4 to -6 moderate; <-6 poor	-3.164
Caco2 permeability (log P_{app} in 10^{-6} cm/s)	>0.9	0.94
Intestinal absorption (human) (%)	>30%	92.416
Distribution		
VDss (human) (log L/kg)	>0.45 well-distributed; <-0.15 poorly distributed	0.524
BBB permeability (log BB)	>0.3 able to cross the BBB; <-1 unable to cross the BBB	-0.727
Metabolism		
CYP2D6 substrate	No	No
CYP3A4 substrate	No	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Excretion		
Total Clearance (log mL/min/kg)	>0.4	1.339
Toxicity		
AMES toxicity	No	No
Hepatotoxicity	No	No
Skin Sensitisation	No	No

3.5. Bioavailability Radar

Considering both efficacy and toxicity, limited bioavailability is frequently identified as a major factor contributing to drug development failures, while oral delivery remains the most common route of administration. Consequently, the oral bioavailability radar chart evaluates drug-likeness using six key physicochemical parameters-lipophilicity, size, polarity, solubility, flexibility, and saturation- to estimate a compound's potential for oral absorption.

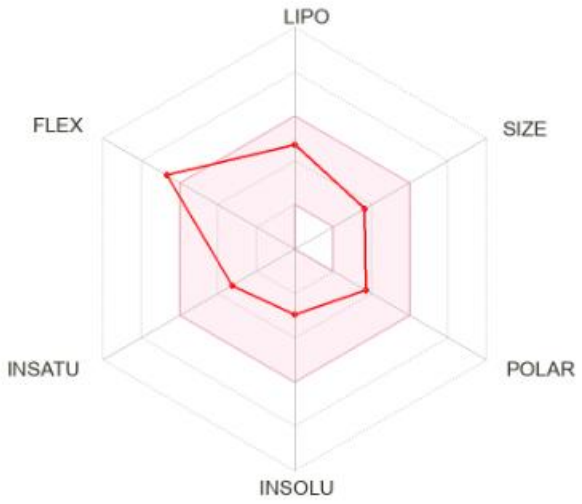

Figure 2. Bioavailability radar of 6-gingerol.

Table 4. Bioavailability radar chart of 6-gingerol

Parameter	Reference range	6-gingerol
Lipophilicity (XLOGP3)	0.7–5.0	2.76
Size (MW)	150–500 (g/mol)	294.39
Polarity (TPSA)	20–130 Å²	66.76
Saturation (Fraction Csp3)	0.25–1	0.59
Solubility (LogS (ESOL))	-6 – 0	-2.96
Flexibility (Num. rotatable bonds)	≤ 9	10

Lipophilicity, molecular weight (MW), TPSA, fraction Csp3, and solubility (LogS) of 6-gingerol fall within the optimal reference range, supporting its drug-like potential. However, the compound exhibits high molecular flexibility (10 rotatable bonds), which may lead to less favorable pharmacokinetic distribution (Table 4, Figure 2). 6-Gingerol shows promising drug-like properties; however, high molecular flexibility may limit its bioavailability.

4. Discussion

The incidence of dyslipidemia has been steadily increasing and is now affecting younger populations, especially young males [18], accompanied by severe cardiovascular complications. In addition to conventional therapeutic approaches such as the administration of statins and fibrates combined with lifestyle modifications, including regular physical activity and dietary fat restriction, naturally derived bioactive compounds with lipid-lowering potential and favorable safety profiles have attracted growing scientific interest.

6-Gingerol, a natural phenolic compound derived from *Zingiber officinale* Roscoe, Zingiberaceae [19], demonstrated moderate binding affinities toward three key targets involved in lipid metabolism: 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), peroxisome proliferator-activated receptor alpha (PPAR-α), and cholesteryl ester transfer protein (CETP). The compound satisfied all five criteria of Lipinski's

rule of five, indicating favorable drug-like properties. Furthermore, 6-gingerol exhibited advantageous pharmacokinetic characteristics and showed no detectable toxicity, suggesting a high degree of safety for therapeutic use. As a bioactive constituent of ginger, 6-gingerol possesses diverse pharmacological effects, including anti-inflammatory, antiviral, antitumor, antioxidant, and antiemetic effects [20]. Taken together, these findings highlight 6-gingerol as a promising natural compound for further investigation and development as a lipid-lowering therapeutic agent.

6-Gingerol exhibited a binding energy of -6.2 kcal/mol with HMG-CoA reductase, indicating its potential to inhibit the enzyme involved in endogenous cholesterol biosynthesis. 6-Gingerol interacted with HMG-CoA reductase through hydrogen bonds (GLU700, LYS606, SER705, HIS635), π-cation interaction (LYS633), which markedly enhances binding affinity, π-alkyl interaction (PRO798), and multiple van der Waals interactions that stabilize its binding at the active site of HMG-CoA reductase (Figure 3A). These interactions suggest that 6-gingerol may mimic the inhibitory mechanism of statins [21], preventing the conversion of HMG-CoA to mevalonate, thereby reducing endogenous cholesterol synthesis. Although the binding energy of 6-gingerol is higher than that of simvastatin (-6.7 kcal/mol), it still demonstrates moderate inhibitory potential, contributing to its lipid-lowering effect when combined with its anti-inflammatory and antioxidant properties [22].

The docking results of 6-gingerol with PPAR-α showed a binding energy of -7.2 kcal/mol, indicating a moderate affinity within the ligand-binding domain of this nuclear receptor. As shown in the interaction diagram (Figure 3B), 6-gingerol establishes multiple conventional hydrogen bonds with TYR464, HIS440, GLN277, and GLU269, together with a carbon–hydrogen bond to PHE351. These directional polar contacts are complemented by several nonpolar stabilizing interactions, including π-alkyl contacts with ILE447, PHE273, and CYS276, a π-sulfur interaction with MET355, and a π-sigma interaction with ILE354. The coexistence of several hydrogen bonds and a network of π-type and hydrophobic interactions suggests both high binding specificity and thermodynamic stability of the complex. The hydrogen bonds provide defined orientation and specificity within the pocket, while the π-alkyl and π-sigma interactions enhance hydrophobic packing and contribute to the overall binding affinity.

PPAR-α plays a central role in regulating lipid metabolism, particularly by enhancing the β-oxidation of fatty acids in the liver. Activation of PPAR-α leads to decreased plasma triglyceride levels through the upregulation of genes involved in fatty acid transport and oxidation. The interaction profile of 6-gingerol indicates that this compound may act as a partial agonist, consistent with previous studies reporting the PPAR-α activating potential of natural compounds [23].

Analysis of the 2D interaction diagram with CETP revealed that 6-gingerol had a binding energy of -6.1 kcal/mol, forming π-alkyl interactions with LE82, VAL84, as well as multiple conventional hydrogen bonds with THR127, SER191, and LEU20 (Figure 3C). CETP is a protein that facilitates the transfer of cholesteryl esters from HDL to LDL, resulting in reduced HDL levels in plasma. Therefore, inhibition of CETP represents a potential strategy to increase HDL concentrations and enhance reverse cholesterol transport. The interaction model of 6-gingerol suggests a mild inhibitory effect on CETP, which may contribute to elevated HDL levels and confer cardioprotective benefits. Moreover, a previous study demonstrated that 10-dehydrogingerdione, another bioactive compound derived from *Zingiber officinale*, exhibited CETP inhibitory activity in a rabbit model, resulting in increased HDL-cholesterol and improved lipid profile [24]. This finding further reinforces the potential of ginger-derived compounds as natural modulators of cholesterol transport and HDL metabolism.

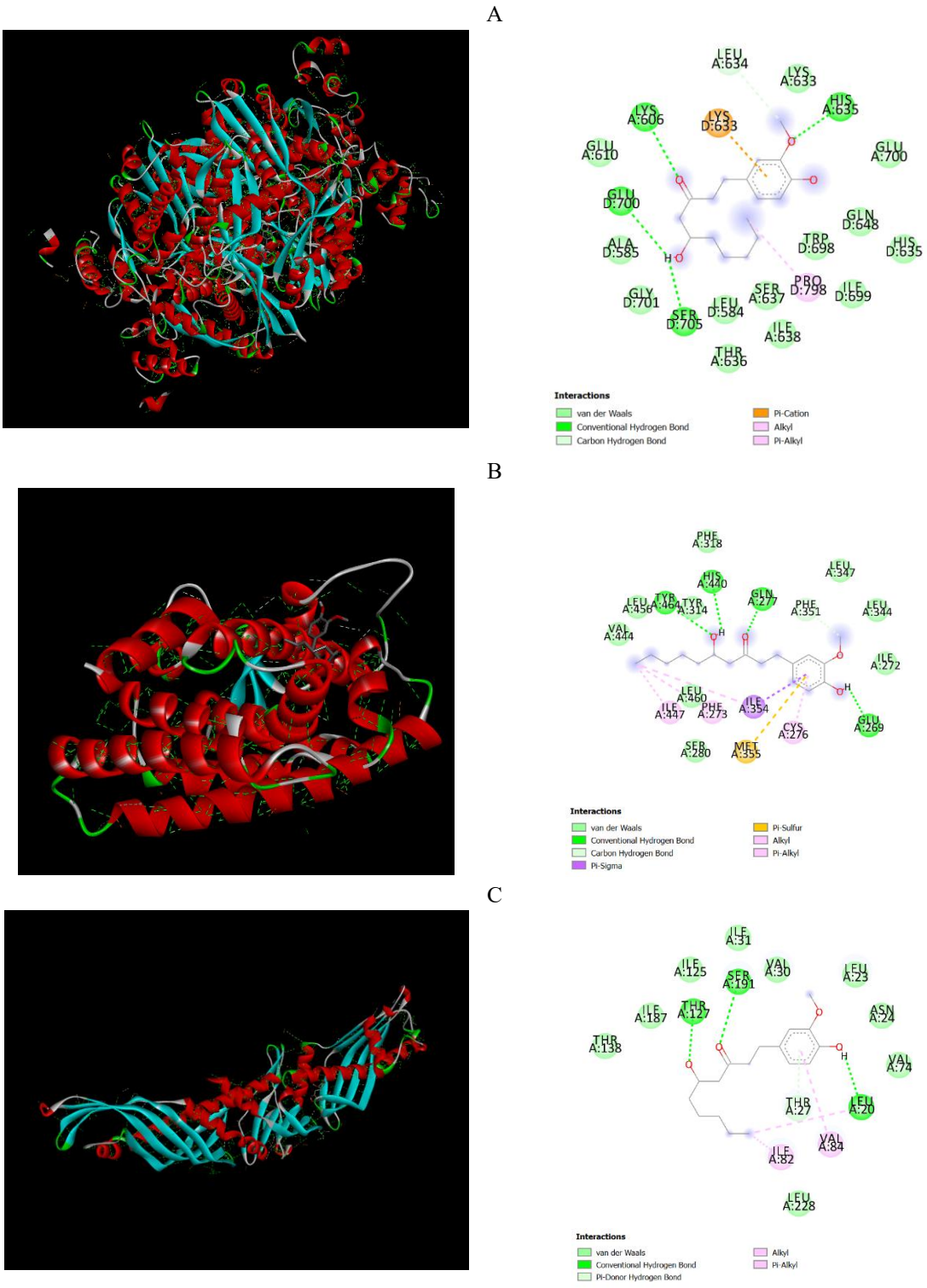

Figure 3. A. Interaction of 6-gingerol with HMG-CoA reductase; B. Interaction of 6-gingerol with PPAR-α; C. Interaction of 6-gingerol with CETP.

As shown in Figure 2 and Table 4, the physicochemical parameters of 6-gingerol largely fall within the optimal range. 6-Gingerol exhibits a molecular weight of 294.39 g/mol, well within the preferred range (150–500 g/mol), suggesting a suitable molecular size for passive diffusion across biological membranes. Its lipophilicity (2.76) reflects balanced hydrophobicity that supports efficient membrane permeability. The compound's topological polar surface area (TPSA = 66.76 Å) is positioned comfortably within the favorable range of 20–130 Å, implying effective intestinal absorption [16].

The fraction of sp^3 carbons (0.59) indicates an adequate degree of saturation, a feature associated with better structural stability [16]. 6-Gingerol also shows good solubility (LogS = −2.96). One parameter slightly outside the optimal range is flexibility, with 10 rotatable bonds (recommended ≤9), as an increased number of rotatable bonds can negatively affect the permeation rate [25]. However, this minor deviation is unlikely to impair bioavailability, as the molecule maintains a favorable overall physicochemical balance. In conclusion, these bioavailability parameters suggest that 6-gingerol exhibits physicochemical properties consistent with favorable oral bioavailability and overall drug-likeness, thereby reinforcing its potential as a safe, well-absorbed, and naturally derived candidate for further development in dyslipidemia management.

Conclusions

In summary, the molecular docking and pharmacokinetic analyses demonstrated that 6-gingerol possesses promising multi-target lipid-lowering potential, acting through moderate inhibition of HMG-CoA reductase, partial activation of PPAR-α, and selective inhibition of CETP. 6-Gingerol meets Lipinski's drug-likeness criteria, exhibits favorable pharmacokinetic properties, and shows no detectable toxicity. Therefore, it emerges as a safe and natural candidate for further development as a complementary or alternative agent in the management of dyslipidemia. Future *in vitro* and *in vivo* investigations are required to validate these *in silico* findings and to clarify the molecular mechanisms underlying its hypolipidemic activity.

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