

MOLECULAR DOCKING AND ADMET ANALYSIS OF CUCURBITACIN B AGAINST HMG-CoA REDUCTASE: A COMPARATIVE IN SILICO STUDY WITH PRAVASTATIN AND IMPLICATIONS FOR LIPID-LOWERING AND PROGERIA MANAGEMENT

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ABSTRACT

Hyperlipidemia and Hutchinson-Gilford Progeria Syndrome (HGPS) are mechanistically distinct disorders that converge at a common metabolic node, the mevalonate pathway, specifically at HMG-CoA reductase. While statins - such as pravastatin, remain the standard inhibitors of this enzyme. A natural triterpenoid, such as cucurbitacin B (a bioactive compound from Cucurbita pepo) have demonstrated diverse pharmacological properties but remain unexplored as HMG-CoA reductase inhibitors. This study aimed to compare the binding affinity, pharmacokinetic profile and toxicity of cucurbitacin B against pravastatin using molecular docking and ADMET analysis. The 3D structures of the both compounds were retrieved from PubChem database and human HMG-CoA reductase was taken as the target for molecular docking. Predictive models including SwissDock and MzDOCK were employed to carry out molecular docking, whereas, the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties were predicted using SwissADME and ProTox 3.0 servers. Cucurbitacin B demonstrated a better binding affinity than pravastatin with a score of -7.398 kcal/mol and -5.858 kcal/mol using SwissDock and a score of -8.2 and -7.7 kcal/mol using MzDOCK respectively. It formed hydrophobic, hydrogen bond, and salt bridge interactions with amino acid residues of the enzyme active site. The ADMET properties of cucurbitacin B were found to be better than those of pravastatin with an exception that it exhibited a higher molecular weight (547.58 versus 406.54 g/mol), higher lipophilicity (4.79 versus 1.27), poor gastrointestinal absorption, but the oral bioavailability of Cucurbitacin B can be improved using advance drug delivery technology like micelles or nanoparticles-based formulation. It was also predicted to have a low oral LD50 (14 mg/kg, class 2) compared to pravastatin (8939 mg/kg, class 6), this highlighting a key safety concern. These findings suggest that cucurbitacin B may represent a potential lead scaffold for HMG-CoA reductase targeted investigation in Hyperlipidemia and HGPS; however, its predicted toxicity highlights the need for further safety evaluation and structural optimization.

KEYWORDS: Cucurbitacin B; Pravastatin; HMG-CoA reductase; Molecular Docking; ADMET; Hutchinson-Gilford Progeria Syndrome; Hyperlipidemia; Mevalonate pathway.

1. INTRODUCTION

1.1 Background on Hyperlipidemia and HGPS

Hyperlipidemia is a cardiac disorder defined by elevated levels of low-density lipoprotein cholesterol and triglycerides in the bloodstream. This disorder is an important risk factor for atherosclerosis, coronary artery disease, and stroke.^[1-4] And this condition is treated using medications that inhibit the synthesis of cholesterol in the liver.^[5] Hutchinson-Gilford Progeria Syndrome (HGPS) is an extremely rare and fatal early-onset aging syndrome resulting from de novo mutations in the LMNA gene, which leads to the formation of a permanent farnesylated form of lamin A protein, called progerin.^[6-8] The accumulation of progerin in the nuclear membrane leads to altered nuclear structure and function, which gives rise to the premature aging phenotype in patients.^[9,10] Although hyperlipidemia and HGPS are mechanistically different disorders, they share one common metabolic point: the mevalonate pathway, particularly the HMG-CoA reductase enzyme.^[11]

1.2 HMG-CoA Reductase as a Drug Target

HMG-CoA reductase is an enzyme that catalyzes the production of mevalonate from HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A), which is the rate-limiting step in the biosynthesis of cholesterol.^[12,13] Therefore, it is the most validated target for lipid-lowering drug discovery. Apart from cholesterol production, the mevalonate pathway is also involved in the synthesis of isoprenoids, such as farnesyl pyrophosphate, which serves as the precursor molecule used in the post-translational modification of proteins, such as prelamin A. Therefore, the inhibition of HMG-CoA reductase leads to decreased production of both cholesterol and farnesyl pyrophosphate.^[14]

1.3 Statins: Standard Therapy in Lipid Lowering and HGPS

Statin is an inhibitor of HMG-CoA reductase and is the first choice for the treatment of hyperlipidemia via blocking of the mevalonate pathway and suppression of cholesterol production.^[15] Pravastatin is hydrophilic and does not penetrate the blood-brain barrier; therefore, it has a good hepatic safety profile. Pravastatin was selected as the reference compound in the present study because of its established HMG-CoA reductase inhibitory activity and its specific clinical-investigational relevance to HGPS.^[16] Pravastatin reduces the production of farnesyl pyrophosphate, which results in the inhibition of the production of isoprenoid intermediates necessary for progerin farnesylation. This mechanism works in addition to the mechanism of action of farnesyltransferase inhibitors (FTIs), which act directly on the inhibition of progerinfarnesylation. Therefore, pravastatin was used together with FTI lonafarnib and bisphosphonate zoledronic acid (ZOPRA therapy) as a multi-target treatment of the process of prenylation on different stages of the mevalonate pathway. A clinical study on 37 children with HGPS revealed good tolerance of the combination of these three

drugs and positive effects on weight gain, echodensity of carotid artery, and bone density, but no additional cardiovascular benefits compared with lonafarnib alone.^[17,18] Experiments showed that pravastatin inhibits the accumulation of progerin in the nucleus and partially restores normal distribution of lamin A in HGPS fibroblasts, which proves the biological importance of this drug in reducing toxicity of progerin. However, current data indicate that pravastatin is safer and more effective as an adjunctive agent with primary effect due to synergistic inhibition of the prenylation pathway in combination with other drugs.^[19]

1.4 Cucurbita pepo and Cucurbitacin

Cucurbita pepo commonly known as pumpkin or squash. It is a nutritious plant which is a member of the Cucurbitaceae family and cultivated in all around the world due to its nutritional and medicinal benefits. Traditionally, various parts of the plant, such as its seeds and fruit, have been used as anthelmintics against parasitic infestation and in the treatment of various urinary problems, inflammation of the bladder, benign prostatic hyperplasia (BPH), kidney disease, gastrointestinal problems, and wound healing. Modern pharmacological studies have validated many of the traditional uses of Cucurbita pepo, including its antioxidant, anti-inflammatory, antimicrobial, antidiabetic, nephroprotective, hepatoprotective, cardioprotective, and anticancer properties. These actions were confirmed by their phytochemicals, including carotenoids, phenolics, sterols, tocopherols, polysaccharides, and triterpenoids.^[20]

Among these bioactive substances, cucurbitacins are a series of highly oxygenated tetracyclic triterpenoids responsible for the characteristic bitter taste of various Cucurbitaceae plants. Currently, more than 20 natural occurring cucurbitacins have been identified, out of which cucurbitacins B, D, E, and I have been extensively studied.^[21,22] Studies performed on these compounds have shown that cucurbitacins have strong anti-inflammatory, antioxidant, antiviral, antifibrotic, and anticancer properties by modulation of signaling pathways, such as JAK/STAT3, PI3K/Akt/mTOR, NF- κ B, and MAPK.^[23] Cucurbitacins have been studied in experimental models of breast cancer, lung cancer, liver cancer, pancreatic cancer, colorectal cancer, prostate cancer, inflammatory disorders, diabetes, obesity, cardiovascular diseases, and neurodegenerative diseases.^[24,25] Among them, cucurbitacin B has received much attention because of its ability to regulate apoptosis, autophagy, oxidative stress, and cellular senescence.^[26] Despite having these multiple pharmacological activities, little is known about the effect of cucurbitacin B on 3-hydroxy-3-methylglutaryl coenzyme A reductase and the mevalonate pathway. Thus, the rationale of the current study.

1.5 Molecular Docking and In Silico Approaches

Molecular docking is an in-silico method used to determine the optimal orientation and binding affinity of a ligand within a specific protein, enzyme, or receptor. ADMET studies (absorption, distribution, metabolism, elimination, and toxicity) together with molecular docking allows researchers to perform an inexpensive preliminary test of candidate compounds before conducting experiments to evaluate their pharmacokinetic properties, drug-likeness, and toxicity profiles.^[27,28] This strategy is extensively applied in drug discovery and drug repurposing for natural product research.^[29,30]

1.6 Rationale and Objective of the Study

Pravastatin is already an accepted drug that has been used in treatment of hyperlipidemia and also been studied in HGPS treatments. The present research aimed to compare Pravastatin with Cucurbitacin B through molecular docking and ADMET study. It was necessary to evaluate the binding affinity of both drugs to HMG-CoA reductase and assess pharmacokinetic properties and toxicity of Cucurbitacin B to check if it may be considered a potential HMG-CoA reductase inhibitor drug for future in lipid-lowering therapy and HGPS management.

2. MATERIALS AND METHODS

2.1 Preparation of Test Drug (Cucurbitacin B)

The three-dimensional structure of cucurbitacin B was retrieved from the PubChem database (PubChem CID: 5281316) in SDF format. The canonical SMILES of cucurbitacin B is CC(=O)OC(C)(C)/C=C/C(=O)[C@@](C)([C@H]1[C@@H](C[C@@]2([C@@]1CC(=O)[C@@]3([C@H]2C=C4[C@H]3C[C@@H](C(=O)C4(C)C)O)C)C)O)O with a molecular formula of $C_{32}H_{46}O_8$ and a molecular weight of 558.70 g/mol. The structure was viewed using the Molegro molecular viewer tool, which was then used for the docking study.^[23]

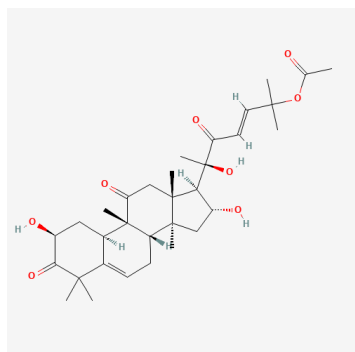


Figure 1: 2D structure image of Cucurbitacin B.

2.2 Preparation of Standard Drug (Pravastatin)

The three-dimensional structure of pravastatin was obtained from PubChem (PubChem CID: 54687) in SDF format. The canonical SMILES of pravastatin is CC[C@H](C)C(=O)O[C@H]1C[C@@H](C=C2[C@H]1[C@H]([C@H](C=C2)C)CC[C@H](C[C@H](CC(=O)O)O)O)O with a molecular formula of $C_{23}H_{36}O_7$ and molecular weight of 424.53 g/mol. The molecule was prepared in the same way as the test compound to maintain consistency in the docking process.

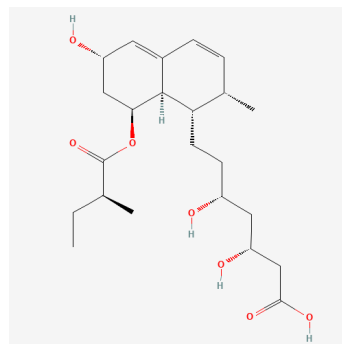


Figure 2: 2D structure image of Pravastatin.

2.3 Target Protein Preparation

The crystal structure of the human HMG-CoA reductase enzyme was retrieved from the RCSB Protein Data Bank (PDB ID: 1HW9), in which the structure was solved at a resolution of 2.33 Å.^[13] In the SwissDock protocol, the extracted structure was processed to isolate the A-chain only; otherwise, all co-crystallized ligands, water molecules, and B, C, and D-chains were removed (by using molegro molecular viewer) to obtain a clean receptor for docking.^[28]



Figure 3: Isolated alpha chain of HMG-CoA reductase enzyme.

In the MzDOCK protocol, the full enzyme structure was preserved to maintain the native binding pocket environment. Hydrogens were added and Kollman charges were assigned during the receptor preparation step, followed by the deletion of water molecules from the crystalline structure. The SIM_A co-crystal ligand was retained for the identification and positioning of the binding site. The binding site for MzDOCK docking was defined around the position occupied by SIM_A.^[31]

2.4 ADMET Analysis

The physicochemical, pharmacokinetic, and medicinal chemistry properties of both molecules were predicted using the SwissADME web server. Toxicological endpoints, including hepatotoxicity, immunotoxicity, mutagenicity, cytotoxicity, LD50, and toxicity

classification, were predicted using ProTox 3.0, which was compared to previous toxicity screening studies.^[32,33]

2.5 Molecular Docking and Interaction Analysis

The Molecular docking study was performed to determine the binding affinity of cucurbitacin B and pravastatin against the HMG-CoA reductase enzyme. In SwissDock software (based on the AutoDock Vina engine), the ligand was submitted as per their canonical SMILES, and the PDB file of the isolated alpha chain of HMG-CoA reductase was uploaded as the target. The docking grid box was centered at coordinates 27, 23, and 5 with dimensions of 25 × 25 × 25 Å, encompassing the catalytic binding pocket. The exhaustiveness parameter was set to 4. The pose with the most favorable binding energy for each molecule was reported.^[28]

MzDOCK was additionally employed for molecular docking and protein-ligand interaction analysis for Cucurbitacin B and Pravastatin with HMG-CoA reductase.^[27,29] The 3D ligand structures were loaded in SDF format, and ligand preparation was performed using the MMFF94 force field at physiological pH (7.4). The prepared ligands were docked against the full structure of the HMG-CoA reductase enzyme. In receptor preparation, hydrogen atoms were added, Kollman charges were assigned, and crystallographic water molecules were deleted. The docking protocol was validated by redocking the native co-crystallized ligand SIM_A into the active site of HMG-CoA reductase after removal from the receptor structure. The docking grid was placed on the position of SIM_A with a buffer size

of 4 Å. MzDOCK docking was performed in mode 9 with an exhaustiveness value of 8. The highest-ranked pose was used for protein-ligand interaction analysis. Protein-ligand interactions were performed to identify hydrophobic, hydrogen bonding, and salt bridge interactions between the docked ligands and HMG-CoA reductase residues. Interacting residues and inter-molecular distances between the residues were recorded, and interaction diagrams in 2D were created for comparison between Cucurbitacin B and Pravastatin.

3. RESULTS AND DISCUSSION

3.1 ADMET Properties Prediction of Statin Analogs

3.1.1 Drug-Likeness Properties

Drug-likeness parameters for pravastatin and cucurbitacin B are summarized in Table 1. Cucurbitacin B (558.70 g/mol) had a higher molecular weight than pravastatin (424.53 g/mol). In addition, cucurbitacin B exhibited a higher consensus LogP (3.10 vs. 2.21), molar refractivity (150.94 vs. 114.04), and topological polar surface area, indicating that cucurbitacin B has greater lipophilicity and a more structurally complex molecular framework. In contrast, pravastatin contained a greater number of rotatable bonds and hydrogen bond donors and acceptors, suggesting that it has higher molecular flexibility. Both molecules showed comparable bioavailability scores (0.55 vs. 0.56). Cucurbitacin B showed a higher synthetic accessibility score (6.79 vs. 5.88), which indicates that its chemical synthesis may be more challenging than that of pravastatin. Neither molecule triggered the PAINS alerts.

Table 1: Drug-likeness predictions for pravastatin and cucurbitacin B as predicted by SwissADME. All derivatives showed no PAINS alerts (score=0).

Molecule	Pravastatin	Cucurbitacin B
Mw	424.53 g/mol	558.70 g/mol
Consensus LogP	2.21	3.10
NR	11	6
HBA	7	8
HBD	4	3
MR	114.04	150.94
TPSA	124.29 Å ²	138.20 Å ²
Bio S.	0.56	0.55
Syn A.	5.88	6.79

Key: PAINS = pan assay interference compounds alert, MW = molecular weight, LogP = octanol/water partition coefficient, NR = number of rotatable bonds, HBA = hydrogen bond acceptors, HBD = hydrogen bond donors, MR = molar refractivity, TPSA = topological polar surface area (Å²), Bio S.= bioavailability score, Syn A. = synthetic accessibility.

3.1.2 Pharmacokinetic Properties

Pharmacokinetic predictions (Table 2) revealed that pravastatin exhibited high gastrointestinal absorption, whereas cucurbitacin B exhibited low GI absorption. The previous studies indicates that the oral bioavailability of Cucurbitacin B can be improved using advance drug delivery technology like micelles or nanoparticles-based

formulation.^[23] Both compounds were predicted to be non-permeable through the blood-brain barrier. Both of these molecules were identified as P-glycoprotein substrates, which implies low central nervous system exposure and possible excretion through transporter proteins. Both compounds were predicted to be inactive for CYP2C19, CYP2C9, and CYP2D6; hence, they do not have a chance of interactions with these metabolic enzymes. It is important to mention that cucurbitacin B was predicted as a potential inhibitor of the CYP3A4 enzyme., which may influence its metabolic profile and warrants further pharmacokinetic evaluation. Skin permeability (log Kp) was slightly more negative for cucurbitacin B (-7.83 cm/s) than pravastatin (-7.12 cm/s), indicating slightly lower dermal permeability.

Table 2: Pharmacokinetic predictions for pravastatin and cucurbitacin B as predicted by SwissADME and Protox 3.0.

Molecule	Pravastatin	Cucurbitacin B
GI absorption	High	Low
BBB permeation	No	No
Pgp substrate	Yes	Yes
CYP2C19 Inhibition	Inactive	Inactive
CYP2C9 Inhibition	Inactive	Inactive
CYP2D6 Inhibition	Inactive	Inactive
CYP3A4 Inhibition	Inactive	Active
log Kp (cm/s)	-7.12 cm/s	-7.83 cm/s

Key: BBB, blood-brain barrier; Pgp, P-glycoprotein; log Kp, skin permeability in cm/s.

3.1.3 Medicinal Chemistry Parameters

The medicinal chemistry assessment (Table 3) showed that Cucurbitacin B satisfied the Muegge and Veber criteria but exhibited one Lipinski violation due to its molecular weight greater than 500 g/mol and three Ghose violations with respect to its molecular weight, molar refractivity and atom count. It also showed one Egan violation because of its high topological polar surface area (TPSA>131.6). Both molecules were free from PAINS (0 alerts) which indicating a low probability of false-positive biological activity. However,

Cucurbitacin B displayed two Brenk alerts which implies the presence of certain structural features that may require optimization during the lead development. During the lead-likeness evaluation, both molecules exceeded the preferred molecular weight limit, whereby Cucurbitacin B displayed one violation and Pravastatin displayed two violations. Overall, these results suggest that even though Cucurbitacin B has some medicinal chemical drawbacks resulting from the structural complexity, These findings indicate that Cucurbitacin B may serve as a lead scaffold for further optimization, although its physicochemical and toxicity liabilities must be addressed before therapeutic development.^[21,23,25]

Table 3: Medicinal chemistry predictions for Pravastatin and Cucurbitacin B as predicted by SwissADME.

Molecule	Pravastatin (Standard)	Cucurbitacin B (Test)
Lipinski	Yes; 0 Violation	Yes; 1 Violation: MW>500
Ghose	Yes	No; 3 Violation: MW>480, MR>130, #Atoms>70
Veber	No; 1 Violation: Rotors>10	Yes
Egan	Yes	NO; 1 Violation: TPSA>131.6
Muegge	Yes	Yes
PAINS	0 alert	0 alert
Brenk	0 alert	2 alerts
Lead-likeness	No; 2 violatio: MW>350, Rotors>7	No; 1 violation: MW>350

Key: MW = molecular weight, MR = Molar Refractivity, TPSA = topological polar surface area (nm²), PAINS = pan assay interference compounds alert.

3.1.4 Toxicity Predictions

ProTox 3.0 toxicity predictions (Table 4) revealed both Pravastatin and Cucurbitacin B to be predicted as inactive for hepatotoxicity, mutagenicity and cytotoxicity, suggesting the absence of these major toxicological liabilities. However, the predicted LD50 value of Cucurbitacin B (14 mg/kg, toxicity class 2) was much lower than that of Pravastatin (8939 mg/kg, toxicity class 6), reflecting the significantly higher acute

toxicity potential of Cucurbitacin B compared to the reference drug. The predicted LD50 should be interpreted as an acute systemic toxicity prediction and should not be directly equated with cell-based cytotoxicity findings reported in previous studies. Therefore, the present toxicity prediction represents an important limitation to the immediate therapeutic interpretation of cucurbitacin B. Thus, its predicted toxicity profile clearly emphasizes the need of further in vitro and in vivo studies for dose optimization and safety evaluation before considering therapeutic application.^[21,23]

Table 4: Toxicity predictions for Pravastatin and Cucurbitacin B as predicted by Protox 3.0.

Compound	Pravastatin	Cucurbitacin B
Hepatotoxicity	Inactive	Inactive
Mutagenicity	Inactive	Inactive
Cytotoxicity	Inactive	Inactive
LD50 (mg/kg)	8939 mg/kg	14 mg/kg
Toxicity class	6	2

3.2 Binding Affinity and Interaction Analysis

3.2.1 Molecular Docking

Molecular Docking of both Pravastatin and Cucurbitacin B against the alpha chain of HMG-CoA reductase resulted in average binding energies which shown in Table 5. The binding energy of Cucurbitacin B (-7.398 kcal/mol) was relatively high when compared to the binding energy of Pravastatin (-5.858 kcal/mol). Additional docking was carried out using MzDOCK to investigate the binding of Cucurbitacin B and Pravastatin at the binding site of complete HMG-CoA reductase - as defined by the position of the ligand used in the co-crystallization, SIM_A. The predicted binding affinity of Cucurbitacin B was found to be -8.2 kcal/mol while that of Pravastatin was -7.7 kcal/mol. This means that

Cucurbitacin B had a better predicted MzDOCK score than the reference compound.

The ranking of Cucurbitacin B and Pravastatin obtained using MzDOCK was similar with SwissDock results, in which Cucurbitacin B was predicted to have a better binding affinity than Pravastatin. However, the scores obtained from MzDOCK and SwissDock were not directly compared as equivalent absolute values because the two workflows use different docking configurations and scoring implementations.^[27] These findings support the possibility that Cucurbitacin B may interact favorably with HMG-CoA reductase and warrant further experimental investigation of its inhibitory activity.^[32,33]

Table 5: Comparison of predicted docking scores for Pravastatin and Cucurbitacin B with HMG-CoA reductase obtained using SwissDock and MzDOCK software.

Molecule	SwissDock Binding Energy [kcal/mol]	MzDock Binding Energy [kcal/mol]
Pravastatin	-5.858	-7.7
Cucurbitacin B	-7.398	-8.2

Note: Docking scores from the two softwares should not be considered as directly equivalent absolute energetic quantities because both are different in the docking workflows and scoring functions. The comparison is primarily intended to assess the consistency of the relative ranking between Cucurbitacin B and Pravastatin.

3.2.2 Interaction Analysis of Cucurbitacin B – HMG CoA reductase complex

The MzDOCK interaction analysis demonstrated that Cucurbitacin B formed multiple non-covalent interactions within the predicted HMG-CoA reductase

binding region. Two hydrophobic interactions were identified with Val683B and Ala856A at distances of 3.63 and 3.62 Å, respectively. Four hydrogen-bond interactions involved Glu559A, Cys561A, Ser565A and Gly860A, with donor-acceptor distances of 3.06, 3.95, 3.05 and 3.54 Å, respectively. In addition, a salt-bridge interaction was observed with Arg568A at a distance of 4.06 Å. The combination of hydrophobic, hydrogen-bond and electrostatic interactions indicates that Cucurbitacin B can establish a diverse network of non-covalent contacts within the predicted binding region of HMG-CoA reductase.

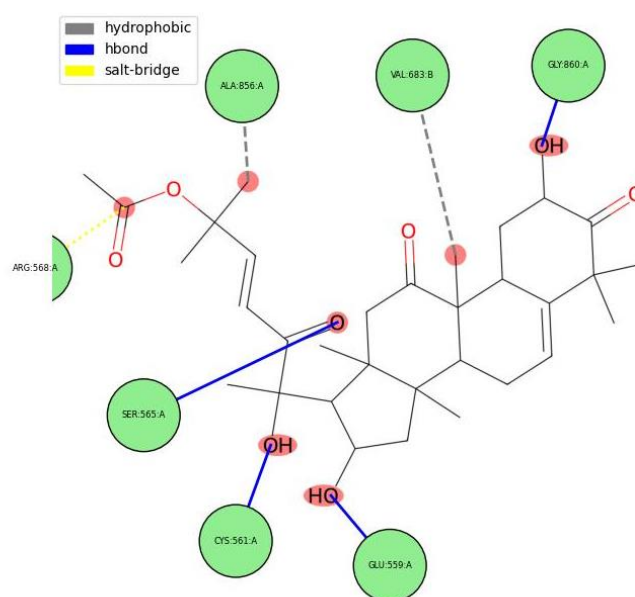


Figure 4: Two-dimensional interaction profile of Cucurbitacin B within the HMG-CoA reductase binding site generated using MzDOCK, showing hydrophobic interactions, hydrogen bonds and salt-bridge interaction with the interacting amino acid residues.

3.2.3 Interaction Analysis of Pravastatin – HMG CoA reductase complex

Pravastatin also exhibited multiple non-covalent interactions within the HMG-CoA reductase binding region. Hydrophobic interactions were observed with Leu562A, Val683B, Leu853A and Leu857A. Hydrogen-

bond interactions involved Ser684B, Asp690B, Lys691B, Lys692B and Asn755A. Additional salt-bridge interactions were identified with Arg590B, Lys692B and Lys735A. These interactions indicate that Pravastatin also forms an extensive network of non-covalent contacts with residues lining the predicted binding region.

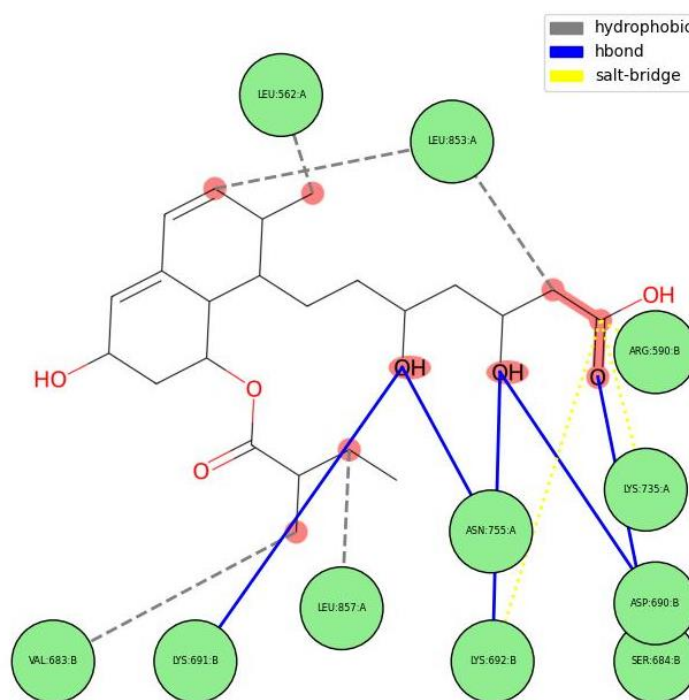


Figure 5: Two-dimensional interaction profile of Pravastatin within the HMG-CoA reductase binding site generated using MzDOCK, showing hydrophobic interactions, hydrogen bonds and salt-bridge interaction with the interacting amino acid residues.

Table 6: Interactions of Cucurbitacin B and Pravastatin with HMG-CoA reductase predicted by MzDOCK.

Cucurbitacin B		
Interaction type	Residue	Distance
Hydrophobic	Val683B	3.63 Å
Hydrophobic	Ala856A	3.62 Å
Hydrogen bond	Glu559A	3.06 Å
Hydrogen bond	Cys561A	3.95 Å
Hydrogen bond	Ser565A	3.05 Å
Hydrogen bond	Gly860A	3.54 Å
Salt bridge	Arg568A	4.06 Å
Pravastatin		
Interaction type	Residue	Distance
Hydrophobic	Leu562A	3.89 Å
Hydrophobic	Val683B	3.63 Å
Hydrophobic	Leu853A	3.62 Å
Hydrophobic	Leu853A	3.32 Å
Hydrophobic	Leu857A	3.58 Å
Hydrogen bond	Ser684B	3.07 Å
Hydrogen bond	Asp690B	4.10 Å
Hydrogen bond	Asp690B	2.88 Å
Hydrogen bond	Lys691B	3.14 Å
Hydrogen bond	Lys692B	3.44 Å
Hydrogen bond	Asn755A	3.05 Å

Salt bridge	Arg590B	4.67 Å
Salt bridge	Lys692B	3.86 Å
Salt bridge	Lys735A	3.28 Å

3.2.5 Comparative Ligand Interaction Analysis

Both compounds exhibited multiple non-covalent interactions with HMG-CoA reductase. Cucurbitacin B formed two hydrophobic contacts, four hydrogen bonds and one salt bridge, whereas Pravastatin exhibited multiple hydrophobic contacts, six hydrogen-bond interactions and three salt bridges. Despite the greater number of individual interactions detected for

Pravastatin, Cucurbitacin B exhibited the more favourable MzDOCK binding affinity (-8.2 kcal/mol Vs -7.7 kcal/mol). This indicates that the overall docking score cannot be interpreted solely from the number of detected interactions, because the energetic contribution, geometry, orientation and spatial arrangement of individual interactions collectively influence the predicted binding score.

Table 7: Summary of MzDOCK interaction profiles.

Parameter	Cucurbitacin B	Pravastatin
MzDOCK affinity	-8.2 kcal/mol	-7.7 kcal/mol
Hydrophobic interactions	2	5
Hydrogen bonds	4	6
Salt bridges	1	3
Overall predicted affinity	More favourable	Less favourable

3.3 Correlation with Previous Studies of Cucurbitacin B

The findings of the present study are consistent with previous experimental evidence demonstrating the various pharmacological ability of **Cucurbitacin B**.^[21–24] The Molecular docking studies provided computational evidence of a favourable interaction of Cucurbitacin B with **HMG-CoA reductase**. SwissDock predicted a stronger binding affinity for Cucurbitacin B (-7.398 kcal/mol) than the reference drug pravastatin (-5.858 kcal/mol), while MzDOCK also ranked Cucurbitacin B more favourably (-8.2 kcal/mol) than Pravastatin (-7.7 kcal/mol). Despite the fact that the docking scores attained using both platforms cannot be directly compared but there is a relative ranking of Cucurbitacin B higher than Pravastatin indicates a favorable interaction of Cucurbitacin B with HMG-CoA reductase, consistent with docking-based evidence for other cucurbitacin family members against distinct enzyme and receptor targets, including cucurbitacin D against colorectal cancer proteins, cucurbitacin I derivatives against the SARS-CoV-2 nucleocapsid protein, and cucurbitacin IIa/IIb against oxidative stress regulatory proteins.^[30,34,35] Furthermore, MzDOCK Interaction analysis revealed that Cucurbitacin B interacts with the HMG-CoA reductase binding region via hydrophobic, hydrogen and salt-bridge interaction. These results suggest that Cucurbitacin B may have potential to interact with the rate-limiting enzyme in mevalonate pathway but it is theoretical only. However, this proposed mechanism remains hypothetical because the present study provides computational evidence of ligand-HMGCR interaction rather than direct experimental evidence of HMGCR inhibition, reduced FPP production, altered progerin prenylation, or improvement of HGPS-associated cellular phenotypes.

Unlike pravastatin, which therapeutic action is mainly targets the modulation of the mevalonate pathway,

Previous published studies highlight the presence of several complementary pharmacological mechanisms for Cucurbitacin B. It inhibits the **de novo lipid synthesis** via inhibition of **ACC**, **FASN**, **SREBP-1** and **PI3K/AKT/mTOR signalling pathway**, an effect directly demonstrated in AKT-driven fatty liver disease and hepatocellular carcinoma models.^[14,36] It also controls the chronic inflammation through inhibition of the **JAK2/STAT3**, **NF-κB**, and **NLRP3 inflammasome pathways** and decrease the oxidative stress through the activation of **Nrf2/HO-1 antioxidant pathway**.^[21,23] Besides, Cucurbitacin B promotes **AMPK activation**, induce **Autophagy**, modulates **mTOR signalling**, triggers **endoplasmic reticulum stress mediated autophagy** and possesses **anti-fibrotic** and **senolytic** activities - thereby improving the cellular homeostasis.^[26,37] Moreover, the **cardioprotective**, **hepatoprotective**, **neuroprotective**, **anti-diabetic**, **anti-obesity**, **anti-tumour** and **anti-cancer properties** of Cucurbitacin B have been demonstrated across multiple experimental systems, including breast cancer, colorectal cancer and neuropsychiatric targets such as monoamine oxidase-A.^[22,24,25,38,39]

However, the toxicity prediction is a main drawback because the Cucurbitacin B had a predicted LD₅₀ value of **14 mg/kg** (Toxicity Class 2) in comparison with **8939 mg/kg** (Toxicity Class 6) for pravastatin – the experimental evidence represent a significant safety limitation and argue against considering unmodified Cucurbitacin B as an immediate therapeutic candidate. The low concentrations of Cucurbitacin B produce No or minimal toxicity in normal cells while remaining effective against affected cells or cancerous cells, whereas the toxicity increases with higher concentration or prolonged use. Furthermore, structurally modified derivatives have been reported to exhibit **47 to 310 times lower toxicity** than the parent compound which indicates that the **dose optimization**, **Structural modification**

and advanced formulation technologies may greatly improve its therapeutic efficacy and safety.^[21,23]

HGPS is a multisystem disease which characterized by chronic inflammation, oxidative stress, metabolic dysfunction, tissue fibrosis, cardiovascular abnormalities and premature cellular senescence.^[6,18,37,40] These pleiotropic mechanisms suggest that Cucurbitacin B have the capability to act on multiple pathological processes simultaneously rather than acting solely through the mevalonate pathway. Therefore, the present docking and interaction findings together with the previously reported pharmacological activities of Cucurbitacin B provide a broader computational and mechanistic rationale for its potential relevance in HGPS.^[27–29,33,38]

4. CONCLUSION

The present study suggests that Cucurbitacin B may represent a potential lead scaffold for further investigation of HMG-CoA reductase-associated mechanisms relevant to HGPS. The computational analysis illustrated favorable interaction with HMG-CoA reductase enzyme while the ADMET prediction showed acceptable drug-like characteristics which includes comparable Bioavailability, absence of blood-brain barrier permeability, P-glycoprotein substrate properties and no predicted PAINS alerts. Despite the facts that the Cucurbitacin B had high molecular weight, increased lipophilicity, poor GI absorption and high synthetic accessibility than the standard drug pravastatin in which the oral bioavailability of Cucurbitacin B can be improved using advance drug delivery technology like micelles or nanoparticles-based formulation. The main concern is the predicted toxicity of Cucurbitacin B with the determined value of LD₅₀ equal to 14 mg/kg (Class 2) comparing to 8939 mg/kg (Class 6) for pravastatin. At the same time, toxicity can be minimized through Dose optimization and Structural modification. Thus, although the present findings provide a solid scientific rationale for the potential application of Cucurbitacin B in HGPS, its therapeutic efficacy and safety should be proven in comprehensive in vitro and in vivo studies and clinical trials.

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